Chemical Hazards to Human Reproduction

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FOR THE

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This report is an evaluation and documentation of the current evidence for reproductive hazards of chemicals, an evaluation of the policy implications of the state of knowledge about chemical hazards to human reproduction, a review of occupational exposures to chemicals that are associated with adverse reproductve effects, and a review of the regulations promulgated to date to control reproductive hazards of chemicals.

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PREFACE

In July 1980, the President's Council on Environmental Quality (CEQ), in cooperation with the Environmental Protection Agency, the National Institute of Environmental Health Sciences, the National Institute for Occupational Safety and Health, and the Occupational Safety and Health Administration contracted with Clement Associates "...to research and evaluate the extant scientific, medical and regulatory literature and documents that relate to the effects of chronic exposure to toxic chemicals and their consequence upon human and animal reproductive integrity, with a view towards authoring a report on this subject." The contract further specified that Clement incorporate into the report the work of two other contractors: (1) a review by Dr. Marion Moses (Mt. Sinai School of Medicine, New York) of occupational exposures to chemicals that are associated with adverse reproductive effects; and (2) a review by Anson M. Keller, Esq., of the regulatory authority, and the regulations promulgated to date, to control reproductive hazards of chemicals. Specifically, Clement was asked to:

1. critically evaluate and document the current evidence for reproductive hazards of chemicals
2. evaluate the policy implications of the state of knowledge about chemical hazards to reproduction
3. integrate into a report the work of the two contractors and the analyses described in 1 and 2.

Adverse reproductive effects that were to be studied included birth defects, low birth weight, fetal wastage (e.g., spontaneous

abortions and stillbirths), failure to conceive (impotence and sterility), and other male and female pathological conditions that affect reproduction. In spite of the broad nature of the charge to Clement, it was agreed that this report would not be a comprehensive critical scientific review, but would be matched to the limited resources that could be assigned to it.

CEQ established an ad hoc advisory panel of scientists with expertise in the area of reproductive toxicity. This panel met at the outset of the project and provided recommendations to CEQ on resource materials, areas of study, and general approaches that would be useful in this initial study and ultimately to CEQ in its further analyses of reproductive hazards.

Dr. Ian C. T. Nisbet, Vice President and Principal Science Advisor of Clement Associates, served as project director, and Dr. Nathan J. Karch, Science Director, served as deputy project director. Dr. Nisbet and Dr. Karch were assisted by other scientists at Clement and by Dr. John A. Thomas, an Associate Scientist at Clement, and Dr. Wayne M. Lednar, an outside consultant.

An initial draft of this report was provided to CEQ on August 15, 1980, and circulated to the advisory panel for review. In addition, CEQ convened a workshop and a number of other meetings to collect information on chronic exposures to chemicals that affect the reproductive integrity of men and women. Comments and material obtained from CEQ and its advisory panel were used by Clement to prepare a revised draft, which Clement then sent to its external reviewers, among whom were Dr. Charles P. Dagg

of the University of Alabama, Dr. Rudolph J. Jaeger of New York University, Dr. Carl Keller of the National Institute of Child Health and Human Development, and Dr. Kenneth J. Rothman of Harvard University. These four consultants provided written comments, and the latter three met with Clement staff to discuss their comments and recommendations for revision. This meeting was attended by Dr. Robert H. Harris, CEQ member, and CEQ staff.

A final draft report was provided to CEQ on November 26, 1980, and circulated by CEQ to its advisory panel and to nearly 100 interested persons in a variety of government agencies, trade associations, public interest groups, and academic institutions. Extensive and detailed written comments were received from many of these parties.

At the conclusion of the comment period, CEQ convened a meeting of its advisory panel to discuss the written comments and their own views and recommendations for revisions.

Clement has endeavored to incorporate the suggested changes, and we believe the report has benefited from the wide range of individuals who have participated in the several stages of review. As is usually the case, it was not possible to reflect all of the views and recommendations of those who submitted comments. Some of the comments were mutually contradictory; some were concerned with the purposes that CEQ intended for the report or the schedule for its completion and distribution; some expressed difficulty in developing an adequate response within the two-week period that was allowed for submitting comments.

Some of the suggestions for change would require substantially more time and resources than were available for this project.

As a result of the succession of expert reviews and the incorporation of the comments and information provided by many knowledgeable and interested parties, this report represents a synthesis of an unusually wide body of information and interpretations. The report is intended first to define the current state of knowledge; second, it is intended to define gaps in information and research needs; and, finally, it is intended as a beginning in the process of identifying the nature and extent of reproductive toxicity, its causes, its relative importance as a public health concern, and further steps that are appropriate to improve our knowledge and understanding.

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EXECUTIVE SUMMARY

Scope of This Report (Chapter I)

This report explores the importance of chemicals as factors contributing to reproductive impairment in the human population. It summarizes the results of studies in exposed humans, surveys methods for testing chemicals in laboratory animals, and discusses the predictive value of animal tests. It also summarizes actions taken to regulate chemical hazards to reproduction, and lists policy issues raised by the facts under review. Although the report is not an exhaustive review of the scientific literature, its findings suggest that the relationship between exposure to chemicals and human reproductive impairment may be an important area of public health concern that deserves more scientific investigation and evaluation.

The Human Reproductive System and its Susceptibility to External Agents (Chapter II)

Human reproduction requires the interaction of complex anatomical, physiological, and behavioral systems, all of which must function unimpaired and in correct sequence if reproduction is to be successful. The first part of Chapter II describes the susceptibility of each stage and process in the male and female systems to the action of toxic chemicals. Table II-1 provides a schematic summary of the types of adverse outcomes (end points) likely to arise from actions at each stage. Action at any one stage may give rise to a number of different end

points, and any one end point can result from a variety of actions occurring at a number of different stages. Further research is needed to extend a knowledge of the inter-relationships among different end points, and between end points and mechanisms of action. Reproduction involves more processes in females than in males, and some processes in females include critical periods of differentiation and development. However, it does not necessarily follow that females are more sensitive to the action of any given agent.

Sources of Statistical Information on the Occurrence of Reproductive Impairments in the U.S. Population (Chapter III)

Chapter III lists a number of large sets of data that are maintained on the frequency of various types of reproductive outcome in the U.S. population, and on the occurrence and distribution of various types of reproductive impairment. Some sets of data are compiled for routine statistical purposes, some for surveillance purposes, and some for research. The primary sources of data are records of vital statistics and physicians' and hospital records. Although complete and accurate data are collected on some types of outcome (e.g., births, birth weight, and infant mortality), data on some outcomes are less reliable (e.g., spontaneous abortions and morphological birth defects), and data are not routinely collected on yet other outcomes (e.g., infertility, early spontaneous abortions and functional impairments). These sets of data are useful in establishing baseline frequencies of occurrence of certain types of impairment, and in revealing

trends and patterns. They are potentially useful for investigating associations between certain types of impairment and "environmental" factors, including chemicals, but they have not often been used for such purposes. The present systems for recording reproductive impairment are limited by problems of reliable ascertainment of the end points and by incomplete reporting. Except for such parameters as birth weight, which is routinely and reliably recorded, it is not clear to what extent data from these systems can be used to investigate small differences in the frequency of specific events. These sets of data would be more useful if they were collected more uniformly and systematically, and if more information were collected to permit linkage between records of adverse outcomes and information on exposure to environmental agents, such as drugs, and occupational factors.

The Magnitude of the Problem of Reproduction Impairments (Chapter III)

Reproductive impairments of one kind or another are both frequent and widespread in the U.S. population. Problems that appear to affect millions of couples at one time or another include inability to conceive, spontaneous abortion, premature births, low birth weight, morphological or functional birth defects, and perinatal mortality. Published estimates of the proportion of reproductive attempts that fail or are impaired in one or more of these ways range approximately from 30% to 80%. The large uncertainty arises primarily from the difficulty in measuring the frequency of conception failures and very early spontaneous

abortions. Further research is needed to clarify the frequency of these outcomes, which may be the most important types of reproductive impairment.

The Contributions of Environmental Factors to Reproductive Impairment in the Human Population (Chapters III and IV)

Chapters III and IV describe evidence suggesting that environmental factors are significantly associated with reproductive impairment in segments of the U.S. population. Environmental factors include nutrition, diet, stress, infections, access to and quality of medical care, radiation, and chemicals such as therapeutic drugs, pesticides, cigarette smoking, alcoholic beverages, illicit and addictive drugs, and industrial pollutants.

a. The frequency of some types of reproductive impairment varies widely from state to state and from county to county within the United States.

b. The frequency of some types of reproductive impairment has changed in time, at a rate much too rapid to be explained by genetic changes or changes in other intrinsic factors.

c. In some cases, the frequency of various kinds of reproductive impairment can be associated statistically with various environmental factors.

d. A number of drugs, chemicals, and other environmental factors have been associated with reproductive impairments in exposed groups within the population.

Evidence of a similar nature is available for various kinds of cancer, and has been used to argue that environmental factors

play a major role in the initiation and development of certain cancers. The evidence of this kind for reproductive impairment is considerably less extensive and complete than that for cancers. However, the evidence summarized in Chapters III and IV suggests that environmental factors (in the broad sense discussed above) are substantial contributors to certain types of reproductive impairment. Further research is needed to establish how important they are, and to distinguish which environmental factors contribute to the occurrence of each type of reproductive impairment.

Reproductive Impairment in the Human Population and the Contribution of Chemicals (Chapters III and IV)

Drugs and other chemicals are only part of the broad spectrum of environmental factors that are known or suspected to impair reproductive success in humans, and there is only limited evidence that can be used to estimate their importance. As yet, large-scale surveillance studies have not been used to identify specific chemical hazards to reproduction (Chapter III). Chapter IV (together with Appendix A) summarizes a large number of studies of the effects of specific agents. The results of these studies suggest that cigarettes and alcoholic beverages have important adverse effects in heavy users and may have substantial effects in moderate users. They also show that certain therapeutic drugs (notably thalidomide and diethylstilbestrol) have had important adverse effects, at least in the past, and that workers exposed in the workplace to certain agents (notably anesthetic gases and lead) are at risk. However, only a limited

number of drugs and occupational exposures have been studied for adverse reproductive effects. The evidence available to date that environmental chemicals may have adverse effects in the general population is scanty and inconclusive, except in cases where accidental contamination of food has resulted in unusually high exposure. However, it is difficult to investigate possible effects of widespread, low-level exposure, and very few studies of such effects have been reported. Further research is needed to establish how many other highly exposed groups are at risk, and whether other general population exposures are significant.

There is much evidence that drugs and other chemicals have had substantial adverse effects on reproduction in highly exposed groups. However, cigarettes and alcohol are the only agents reported to have substantial effects in the general population.

Limitations on Human Studies (Chapter IV)

Chapter IV includes a description of the types of study that are used to identify reproductive hazards in human populations, and a brief discussion of their limitations. The practicality of conducting such studies depends generally on the ability to identify an exposed group and document its exposure. This is generally easiest for prescription drugs, whose use is usually recorded; relatively easy for cigarette smoking and alcohol, for which individuals determine their own pattern of use and can document it fairly reliably; fairly difficult for occupational exposures, for which exposed individuals can usually

be identified but for which the magnitude of exposure is usually difficult to estimate; and very difficult for environmental chemicals, for which both the distribution and magnitude of exposures are difficult to document. Even when exposed groups can be identified, it is often difficult to investigate their reproductive performance unless the affected individuals are willing to discuss these issues with researchers. Other practical problems are common to all epidemiologic studies, including problems encountered in selecting appropriate control groups and documenting their exposure, problems of bias, and confounding factors. For these reasons the most effective studies have been of the effects of drugs; studies of occupational and environmental agents have often been controversial or inconclusive.

Provided that attention is paid to these problems, further studies of highly exposed groups are likely to be useful in identifying specific risk factors. Human epidemiologic studies of industrial groups may be an effective way to establish the safety or hazard of specific chemicals. However, it should be recognized that such studies are inherently difficult to conduct with general environmental pollutants, and that any effects that such agents may be causing in the population are unlikely to be identifiable unless they are unusually conspicuous.

Laboratory Screening Systems (Chapter V)

Chapter V lists a large number of laboratory tests for investigating possible adverse effects of chemical agents on

reproduction. However, at present only three of these tests are in general use for screening chemical agents; these are applied primarily to drugs, food additives, and pesticides. They are expensive to conduct--especially when they have to be run in several species, as part of a multispecies screen--and it is not feasible to apply them to more than a limited number of the potentially toxic chemicals already in the environment or proposed for new uses. In fact, much of our knowledge of the effects in animals of chemicals known to affect reproduction in humans is derived from shorter or simpler tests (see Appendix A).

One important element that is lacking from the existing screening system is a technique for prescreening chemicals, in order to select for full-scale testing those that are most likely to prove hazardous. Such a technique might involve a simple, rapid, in vitro test (analogous to the Ames test for mutagenicity), or application of structure-activity theories to predict likely activity. Although a number of in vitro tests are already available, none appears to be a very strong candidate for this prescreening function. More research and development are needed to improve the efficiency, reliability, and sensitivity of the existing screening systems.

The Use of Laboratory Tests to Predict Human Risks (Chapter VI)

Until more studies can be carried out in exposed groups within the human population, reliance must be placed on laboratory tests to identify potentially hazardous agents. Chapter VI

presents a preliminary analysis of the concordance between the results of experimental studies in animals and the reported effects of the same agents in humans. This analysis is based on data for 21 selected agents, as tabulated in Appendix A. The results of this analysis suggest that many (if not most) reproductive impairments identified in humans have close counterparts in one or more species of experimental animals. That is, specific chemical agents that have been found to be teratogenic or to cause other reproductive impairments in humans have been found to produce qualitatively similar effects in one or more test animal species. Furthermore, there is some agreement between the doses reported to be effective in humans and the doses that are effective in the most sensitive animals (see Tables VI-4 and VI-5). With one exception, humans appear to be somewhat more susceptible than the most susceptible animal species tested.

More detailed analysis is needed to confirm or to modify these preliminary findings. Pending such analysis, they tend to suggest that animal tests can predict both the types of effect likely to occur in humans and (to an order of magnitude) the likely range of effective doses, provided that the appropriate species are selected for testing. These findings show promise for the development of methods for quantitative risk assessment. However, it will be difficult to determine in advance which animal species is appropriate in each specific case, and such a predictive system is liable to yield an unknown number of

"false positive" predictions of hazards. The development of a reliable multispecies screening system will require more data on effects in humans and more research in comparative toxicology, including studies in comparative metabolism and pharmacokinetics.

Dose-response Relationships and Risk Assessment (Chapter VI)

Very little has been published on dose-response relationships for agents that affect reproduction in humans, although such relationships could probably be constructed from data available on the effects of cigarette smoking and alcohol. There appears to be no systematic compilation of dose-response relationships in animals. For teratogenic agents, dose-response relationships in animals usually rise steeply after the dose required to produce the first effect is exceeded. This empirical generalization has been used to argue that threshold (safe) doses usually exist for teratogens in animals. However, it is not clear that the assumption of thresholds can be applied automatically to humans. More research is needed to establish the characteristics of dose-response relationships in humans, and to establish in what circumstances thresholds can be assumed to exist. Such information is required for risk assessments at doses lower than those at which effects have been observed, and for estimating "safe" or "acceptable" levels of exposure.

Regulatory Authority and Regulatory Actions to Date

The federal government has authority under a number of different statutes to regulate chemicals that pose hazards to

human reproduction. Together with statutes that cover specific classes of chemicals or specific exposure situations, the Toxic Substances Control Act (TSCA) confers authority to regulate essentially all manufactured chemicals. However, TSCA excludes three important classes of chemicals that are known or suspected to pose reproductive hazards: tobacco products, alcoholic beverages, and illicit drugs. Under most of the statutes, the authority to regulate chemicals that pose reproductive hazards is part of a general authority to regulate agents that pose health risks, but some statutes (including TSCA) specify teratogenicity as an effect of especial concern.

Despite this broad authority, only a limited number of regulatory actions have been taken specifically to reduce reproductive risks. The most extensive such actions are those of the U.S. Food and Drug Administration (FDA), which has required labeling of agents known to be teratogenic and will shortly require informational packaging with agents known to pose other reproductive hazards. In a number of regulatory actions, information on reproductive effects was cited in support of the action but appeared to be secondary to information on carcinogenic effects. Recent regulatory actions in which reproductive effects were the primary basis for regulation included: diethylstilbestrol, whose approval for use as an animal drug was withdrawn by FDA; lead, for which a new occupational exposure standard was set by the Occupational Safety and Health Administration; and caffeine, for which FDA has proposed to delete its status as a permitted

food additive and to require further testing. In addition, tolerances set for residues of pesticides in food by the U.S. Environmental Protection Agency in some cases, have been based on data on reproductive toxicity, but the methods for establishing tolerances are now under review by the agency. In general, however, regulatory agencies have placed little weight on reproductive toxicity, devoting much more attention to the regulation of carcinogens. The reasons for this lack of emphasis on regulation of reproductive hazards have not been made explicit.

Policy Issues (Chapter VII)

A number of important policy issues are raised by these findings, including the following:

- the importance of reproductive impairments as a public health problem
- the role played by chemicals in reproductive impairment
- the reliability of existing methods for identifying chemical hazards to reproduction
- the lack of accepted procedures for risk assessment
- the scientific basis for regulatory actions
- the differential regulation of exposure to men and women

Parallel between Reproductive Hazards and Carcinogenic Hazards (Chapter VII)

The present state of scientific knowledge of chemical hazards to reproduction is somewhat similar to that of chemical carcinogens in the late 1960s. If scientific knowledge of reproductive hazards is developed in an orderly manner, there is an opportunity to avoid some of the controversies that have been raised by regulation of chemical carcinogens.

Key Findings and Recommendations

- This report explores the importance of chemicals as factors contributing to reproductive impairment in the human population. Although it is not an exhaustive review of the scientific literature, its findings suggest that the relationship between exposure to chemicals and human reproductive impairment may be an important area of public health concern. This area deserves more scientific investigation and evaluation. The study recently initiated by the Interagency Regulatory Liaison Group is expected to provide critical and comprehensive reviews of teratological and other data on reproductive hazards. These reviews would be useful and timely.

- Toxic chemicals can exert effects at many different stages in male and female reproduction. Action at any one stage can give rise to a number of different end points, and any one end point can result from a variety of actions occurring at a number of different stages. Although more stages of reproduction occur in females, including critical processes of differentiation and development, it does not necessarily follow that females are more sensitive to any given agent.

- A number of large sets of statistical data are maintained on the frequency and distribution of various types of reproductive outcome. These sets of data are of varying completeness and accuracy, and cover only certain types of impairment. They have not often been used to investigate associations with external factors, but are useful in establishing baseline data and in revealing trends and patterns. These sets of data would be more useful if they were collected more uniformly, and if more information on environmental factors were collected.

- Reproductive impairments of one kind or another are both frequent and widespread in the U.S. population. Published estimates of the proportion of reproductive attempts that fail or are impaired range approximately from 30% to 80%. Further research is needed to determine the frequency of conception failures and very early spontaneous abortions.

- Evidence derived from geographical patterns, time trends, and associations with specific environmental factors suggests that environmental factors are substantial contributors to certain types of reproductive impairment. However, this evidence is considerably less extensive than the similar evidence for the importance of environmental factors in cancer. Further research is needed to establish the importance of environmental factors in reproductive impairment.

- There is much evidence that drugs and other chemicals have had substantial adverse effects on reproduction in highly

exposed groups. However, cigarette smoking and alcohol are the only effects reported to have substantial effects in the general population.

- The practicality of conducting studies in human populations depends on the ability to identify an exposed group and document its exposure. Other problems encountered in human studies involve the selection of appropriate control groups, elimination of bias and identification of confounding factors. The most effective studies have been those on the effects of drugs; studies of occupational and environmental agents have often been controversial or inconclusive. Further studies of highly exposed groups are likely to be useful in identifying specific risk factors, but such studies are inherently difficult to conduct with general environmental pollutants.

- A large number of laboratory tests is available for investigating possible adverse effects of chemical agents on reproduction. However, only three of these tests are in general use for screening chemical agents. More research and development are needed to improve the efficiency, reliability, and sensitivity of the existing screening systems, and in particular to devise a useful short-term prescreening test.

- A preliminary study of data on 21 chemical agents shows a reasonably close concordance between effects reported in humans and in one or more experimental animal species. With one exception, humans were affected at doses similar to or less than those that affected the most sensitive animals. These findings show promise for the development of methods for quantitative risk assessment. However, it will be difficult to determine in advance which species should be regarded as appropriate for predicting likely effects in humans. Any predictive system based on animal tests may yield an unknown number of "false positive" predictions of hazard. The development of a reliable predictive system will require more research in epidemiology and in comparative toxicology.

- Very little has been published on dose-response relationships for agents that affect reproduction in humans. More research is needed to establish their characteristics, and to establish in what circumstances threshold doses can be assumed to exist. Such information is needed for low-dose risk assessments, and for estimating "safe" or "acceptable" levels of exposure.

- The federal government has broad authority to regulate chemicals that pose reproductive hazards. Apart from labeling of prescription drugs, however, regulatory agencies have placed relatively little emphasis on reproductive hazards in their recent actions. The reasons for this have not been made explicit.

- A number of important policy issues are raised by these findings, including the following:
  - the importance of reproductive impairments as a public health problem
  - the role played by chemicals in reproductive impairment
  - the reliability of existing methods for identifying chemical hazards to reproduction
  - the lack of accepted procedures for risk assessment
  - the scientific basis for regulatory actions
  - the differential regulation of exposure to men and women
- The present state of scientific knowledge of chemical hazards to reproduction is somewhat similar to that of chemical carcinogens in the late 1960s. If scientific knowledge of reproductive hazards were developed in an orderly manner, there would be an opportunity to avoid some of the controversies that have been raised by regulation of chemical carcinogens.

I. INTRODUCTION

Evidence collected during the past four decades has indicated that exposure to certain physical, infectious, and chemical agents is associated with reproductive impairment in humans and laboratory animals. Despite these clear associations, the overall importance of these agents to the human population is difficult to establish. In particular, most chemicals to which humans are exposed have not been tested for effects on reproduction. Of approximately 55,000 chemical substances and mixtures in commercial production (not including drugs, pesticides, food additives, and other minor classes), few have been thoroughly tested for reproductive effects (USEPA 1978, 1980). In addition, there are uncountable numbers of chemicals and complex mixtures that have not been tested in food, water, and air. The number of single chemicals and mixtures that has been tested to date is too small to estimate the proportion that may pose potential hazards to reproduction at levels to which humans are commonly exposed.

This report explores the importance of chemicals as factors contributing to reproductive impairment in the human population. It summarizes the scientific literature on chemical agents known or suspected to affect human reproduction, surveys methods used to test chemicals for reproductive toxicity in animals, and discusses the scientific basis for the use of experimental studies in animals to predict human risks. It also includes

a survey of the legal authorities available to the government to regulate chemicals that pose reproductive hazards, and of the regulatory actions that have been taken to date. Although the report includes extensive scientific documentation, its primary purpose is to define public policy issues rather than to review the state of scientific knowledge about mechanisms of action. A number of policy issues that are raised by existing scientific data on reproductive hazards are listed, but no attempt is made in this report to resolve these policy issues or to recommend government actions (other than additional research).

"Reproductive impairment" is defined broadly in this report to include all effects resulting from parental exposure that interfere with the conception, gestation, birth, and development of offspring to healthy adult life (see Chapter II). It thus includes effects on behavior and fertility of the parents, and effects (such as behavioral impairment, infertility, and cancer) that may not be manifested until the offspring reach adult life. It does not include genetic or chromosomal effects in parents unless there is reason to associate them with other types of reproductive impairment. Although they probably indicate the potential for effects in germ cells, chromosomal effects in somatic cells as a result of parental exposure have no direct impact on reproduction.

This report is concerned primarily with the effects of chemical agents, including therapeutic drugs, pesticides, food additives, cosmetics, cigarette smoking, alcoholic beverages,

illicit and addictive drugs, industrial chemicals, chemicals in consumer products, and environmental pollutants. It does not consider nutritional aspects of food, radiation (on whose effects there is extensive scientific literature), or infectious agents (although agents such as rubella virus are known to be significant causes of birth defects). It is important to emphasize that the chemical agents considered in this report are only part of a wide spectrum of external factors--sometimes referred to us "environmental factors"--that are known to affect human reproduction. Those external factors that are not included here include nutrition, diet, climate, stress, infections and other health factors, access to and quality of medical care, sexual activity, and radiation. Some of the data cited in Chapter III provide evidence that human reproductive impairment is associated with "environmental" factors in this broad sense, but do not provide specific evidence for association with exposure to chemical agents.

Because of time and resource constraints, this report is neither a comprehensive survey of all the information on reproductive hazards nor an intensive, critical review of the scientific literature (see Preface). Since the report is concerned primarily with hazards to human reproduction, no attempt has been made to review the extensive literature on effects of chemicals or reproduction in experimental animals, including the test data on drugs, pesticides, and food additives. The analysis in Chapter VI is based on review of data for a representative

sample of 21 chemicals (Appendix A). An attempt was made to use review papers as primary sources of data, but many of the existing reviews proved to be insufficiently complete or critical for this purpose. Hence this report is generally based on examination of primary scientific literature, with a few exceptions when authoritative reviews were available (e.g., the sections on tobacco smoking and some of the material on drugs included in Tables IV-2 to IV-4) or when only abstracts were obtainable (e.g., the Russian literature cited in Tables IV-5 and IV-6).

The scientific information available on chemicals that pose hazards to human reproduction varies widely in quantity and quality. Scientific reviews, comments by reviewers of drafts of this report, and our own analysis have shown that many of the published reports of chemical hazards are inconclusive or at least questionable. This report does not attempt to make critical evaluations of disputed findings, except to report them as "probable," "possible," "questionable," or "inconclusive." In a policy-oriented report, it is more approriate to draw attention to inconclusive findings, and to the need for further study to resolve them, than to risk understating the problem by omitting them or overstating it by reporting them as definitive.

This report covers a wider range of topics than previous reviews cited herein. Because of its limited depth, its findings are of a preliminary nature, but they appear at least to be

of sufficient importance to demonstrate the value of conducting more critical and comprehensive reviews. In September 1980, the Interagency Regulatory Liaison Group announced the formation of the Task Group on Reproductive Toxicity Risk Assessment and published a work plan that includes critical and comprehensive reviews of a number of topics included in this report (IRLG 1980). However, the work plan is limited to certain aspects of risk assessment, and its purpose is "to develop criteria to support consistent interpretation and utilization of teratological data by each of the IRLG agencies" and of data on other reproductive hazards. The findings in this report indicate that the relationship between exposure to chemicals and human reproductive impairment may be an important area of public health concern. This area deserves more scientific investigation and evaluation, and reviews of aspects of the problem other than teratology would be both useful and timely. In this report, we are concerned with the assessment of reproductive risks from exposure to chemicals, the available information on the importance of chemicals, and the policy issues raised by the nature and extent of scientific knowledge about reproductive hazards.

II. THE HUMAN REPRODUCTIVE SYSTEM AND ITS SUSCEPTIBILITY TO TOXIC CHEMICALS

Studies of the effects of toxic chemicals on human reproduction have been focused heavily on associations between maternal exposure during pregnancy and subsequent birth defects in the offspring. Reproductive effects resulting from exposure of parents at other stages in their lives have not been examined as intensively. In particular, few studies have been conducted on the effects of exposure of men to toxic chemicals on their sperm production or pregnancy outcome in their wives. This chapter describes the stages in the reproductive process in males and females that are susceptible to chemical insult and the types of adverse outcomes that result from effects at various stages.

Susceptibility of the male reproductive system

A number of chemical agents have been shown to impair reproduction in male humans and laboratory animals. Agents such as heavy metals, pesticides, solvents, food additives and contaminants, alkylating agents, antibiotics, and synthetic steroids have been shown to cause infertility in males as well as adverse pregnancy outcomes resulting from mutations in male germ cells (Manson 1978). The main cellular constituents of the testis--the Sertoli, Leydig, and germ cells--are susceptible to chemical modification. Control of germ cell differentiation

is mediated by the Sertoli cells. Antifertility agents, hypophysectomy, and even the normal responses of the testes to steroid hormones may first affect Sertoli cells, and, hence, influence the germ cells (Dym et al. 1977). Leydig cells are the primary source of testosterone, which controls the activity of accessory sex organs and development of secondary sexual characteristics (Connell and Connell 1977).

The function of the testes is controlled by at least two pituitary hormones, luteinizing hormone (LH) and follicle-stimulating hormone (FSH). LH stimulates Leydig cells to synthesize steroid hormones, principally testosterone, and FSH influences the Sertoli cells in initiation of spermatogenesis and maintenance of optimal testicular function (Dufau and Means 1974, Means 1977). Elevation in FSH concentrations can be prognostic of damage to the germ cells or reduced sperm concentration (Setchell et al. 1977). Toxic agents can modify the processes that regulate hormone levels and, hence, can affect sperm production and function.

The process of spermatogenesis occurs in distinct stages that are differentially sensitive to toxic agents. Stem cells, or spermatogonia, proliferate by mitosis to produce new stem cells, some of which differentiate into spermatocytes. Spermatocytes undergo meiotic divisions to produce spermatids, which lose most of their cytoplasm and undergo transformation into spermatozoa. During transportation from the testes to the ejaculatory duct through the epididymis, sperm mature and acquire motility.

Male germ cells are susceptible to chemical agents at each of these stages of spermatogenesis. Spermatotoxic agents can kill the developing sperm cells, cause heritable alterations in them, or cause nonheritable changes in their morphology or function. A permeability barrier between the blood and testes limits the passage of some chemicals into the Sertoli cells (Manson and Simons 1979).

Semen can serve as a route of excretion of chemical agents. The motility and viability of sperm can be influenced by the presence of chemical agents in the seminal plasma (Peterson and Freund 1975). In addition, chemicals in the semen can be transmitted to the female during intercourse and absorbed through the vaginal mucosa. This might lead to pharmacologic effects on the female or on the embryo if the female is pregnant.

Reduction in sperm count may lead to infertility, and production of mutated sperm can cause adverse pregnancy outcome if the mutated sperm fertilizes an egg. In the latter case, the most likely pregnancy outcome is early spontaneous abortion. Other, less frequent outcomes include stillbirths, birth defects, neonatal mortality, and genetic diseases in the offspring. Toxic agents can also affect reproductive functions in males by reducing libido or causing impotence.

Susceptibility of the female reproductive system

In the female, toxic agents can modify the processes of oogenesis as well as other stages in reproduction. At the time of birth, the ovaries contain a full complement of primary

oocytes, which do not undergo further cytogenetic alteration until puberty, when ovulation first occurs. Under the influence of FSH and LH, a secondary oocyte is produced and ovulated. The next cell division goes to completion only after a sperm has penetrated the egg.

More than 400-500 eggs are ovulated during the life span of a woman (Biggers 1979). Many of the primary oocytes present in the ovary at birth undergo degeneration (atresia) before puberty is reached. Treatment with certain chemical agents, especially polycyclic aromatic hydrocarbons, has been shown to accelerate this process, leading to destruction of up to 87% of primary oocytes (Mattison and Thorgeirsson 1978). This can lead to premature onset of menopause and, at least in mice, may precede the development of ovarian granulosa cell tumors (Mattison and Thorgeirsson 1978).

Damage to primary oocytes often results in cell death, but oocytes that sustain genetic damage while in the preovulatory stage can be fertilized. If secondary oocytes that have been treated with alkylating agents just before ovulation are fertilized, they can result in embryos that abort early in development (Basler et al. 1976). Most genetically damaged oocytes that become fertilized result in embryos that die in the implantation or early postimplantation period. It is possible that a small percentage of these embryos survive to term, and these may have malformations and congenital childhood diseases (Basler et al. 1976).

Toxic agents may also modify the processes that regulate hormone levels and, hence, may affect a number of different reproductive functions, including the onset of puberty, ovulation, menstrual cycling, capacitation of sperm prior to conception, and implantation. In addition, the development and functioning of the placenta can be affected by toxic chemicals either directly or as a result of modification in hormone levels.

Prenatal susceptibility to chemical insult

The prenatal organism is susceptible to chemical insult at each stage of the complex developmental process, including the preimplantation, embryonic, fetal, and perinatal periods. In the preimplantation period, fertilization, blastulation, gastrulation, and early erosion of the uterine wall take place. Chemical insult at this stage can lead to embryonic death, but rarely to teratogenic effects. The preimplantation period occurs during approximately the first 3 weeks of human development and the first 6 days of rodent gestation (Wilson and Fraser 1977a).

During the embryonic period, the process of organogenesis occurs from approximately the 3rd to 8th week of gestation in humans and from the 7th to 16th day in rodents (see Table V-5). Organogenesis is characterized by the migration and association of cells and tissues into organ rudiments and is a period of particular vulnerability for induction of structural defects in the embryo. Establishment of the basic organizational patterns of the organ systems occurs during this time (Wilson and Fraser

1977a). Insult during organogenesis can be repaired, or it can lead to birth defects or embryonic death. Individual organ systems have a relatively narrow time span of vulnerability, and the same teratogenic agent can induce different malformations, depending on when the agent is given (Wilson and Fraser 1977a).

Histogenesis, functional maturation, and growth are the major processes occurring during the fetal period. Chemical insult during the fetal period can lead to a broad spectrum of effects from growth retardation to functional disorders or transplacental induction of cancer. The latter two effects are difficult to measure, because long latency periods are often required for their detection. The fetus is more resistant to lethal effects than is the embryo, but exposure to toxic chemicals can lead to stillbirths. The placenta acts as a partial barrier limiting the exposure of the fetus to chemicals absorbed by the mother. The placenta also protects the fetus by metabolizing chemicals, generally to less toxic forms. However, in some cases, such metabolism may activate chemicals to more toxic metabolites, including mutagens and carcinogens. The development in the fetus of enzyme systems that metabolize foreign chemicals is slow and is not completed until after birth.

Structural and functional maturation continues after birth, particularly in the nervous, immune, endocrine, reproductive, and drug detoxification systems. The neonate remains susceptible to chemical insult, especially through exposure to toxic agents

in breast milk. The types of damage most extensively studied, after chemical exposure during the neonatal period, are alterations of the nervous system, reflected in neurobehavioral deficits and childhood cancer.

Relationship between site of action and observable adverse outcome

The foregoing discussion has shown that toxic agents can act by a number of mechanisms at a variety of stages in the male and female. Table II-1 lists the stages and processes in reproduction for which the effects of toxic agents are better documented. It also lists the adverse outcomes (end points) that are most likely to be observed as a result of effects at each stage. This table is incomplete and somewhat oversimplified, because the susceptibility to toxic agents at various stages in reproduction is not well understood. However, Table II-1 demonstrates that effects taking place at any one stage may give rise to several different end points; likewise any one type of end point may result from several different types of effects. This circumstance complicates the interpretation of epidemiologic and toxicologic studies, because a measured end point does not provide unambiguous information about the mechanism or stage of action.

Another complicating factor is that the nature of the adverse outcome may depend on the magnitude of the dose. For example, an agent that exerts a toxic effect on fetal development may give rise to functional deficits at low doses, to birth defects at intermediate doses, and embryonic deaths at high

TABLE II-1

RELATIONSHIP BETWEEN THE SITE AND TIMING OF ACTION OF TOXIC AGENTS ON HUMAN REPRODUCTIVE SYSTEM AND THE OBSERVABLE EFFECTS (END POINTS)

Reproductive Stage	Organs and functions potentially affected		Possible End points
	Female	Male	
Germ cell formation	Oogenesis (occurs during fetal development of mother) Gene replication Cell division	Spermatogenesis Gene replication Cell division	Sterility, subfecundity, damaged sperm or eggs, chromosomal aberrations, menstrual effects, age at menopause, hormone imbalances, changes in sex ratio
	Egg maturation Hormonal influence on ovary	Sperm maturation Sertoli cell influence Hormonal influence on testes	
	Ovulation Hormonal influence on ovary		
Fertilization	Oviduct Contractility Secretions Hormonal influence on secretory and muscle cells	Accessory glands Sperm motility and nutrition Hormonal influence on glands	Impotence, sterility, subfecundity, chromosomal aberrations, changes in sex ratio, reduced sperm function

TABLE II-1 (continued)

Reproductive Stage	Organs and functions potentially affected: Female	Organs and functions potentially affected: Male	Possible End Points
Fertilization (continued)	Uterus Contractility Secretions Hormonal influence on secretory and muscle cells Nervous system Behavior Libido	Nervous system Erection Ejaculation Behavior Libido	
Implantation	Uterus Changes in uterine lining Secretions Hormonal influence on secretory cells		Spontaneous abortion, fetal resorption, chromosomal aberrations, subfecundity, stillbirths, low birth weight

TABLE II-1 (continued)

Reproductive Stage	Organs and functions potentially affected: Female	Organs and functions potentially affected: Male	Possible End Points
Embryogenesis	Uterus Placenta formation		Spontaneous abortion, other fetal losses, birth defects, chromosomal abnormalities change in sex ratio, stillbirths, low birth weight
	Embryo Cell division Tissue differentiation Hormone production Growth		
Organogenesis	Placenta Nutrient transfer Hormone production Protection from toxic agents		Birth defects, spontaneous aborton and other fetal death, chromosomal aberrations, retarded growth and development, transplacental carcinogenesis
	Embryo Organ development and placement Growth		
	Maternal nutrition		

TABLE II-1 (continued)

Reproductive Stage	Organs and functions potentially affected: Female	Organs and functions potentially affected: Male	Possible End Points
Perinatal	Fetus Growth and development Uterus Contractility Hormonal effects on muscle cells Maternal nutrition		Premature births, birth defects, (particularly nervous system), stillbirths, neonatal death, low birth weight toxic syndromes or withdrawal symptoms in neonates
Postnatal	Infant survival Lactation		Mental retardation, infant mortality, retarded development, metabolic and functional disorders, developmental disabilities (e.g., cerebral palsy and epilepsy)

doses. Furthermore, such end points as birth defects may arise from maternal exposure to chemicals transmitted in semen or from damaged sperm. Thus, impairments generally associated with a stage in reproduction that occurs in the female may actually be the result of exposure in the male.

Differences in susceptibility between males and females

Although there are parallels between the male and female reproductive processes up to the stage of germ cell formation, most of the reproductive processes thereafter take place in the female. The female-placenta-fetus system has many stages at which toxic agents can act that have no counterpart in the male (see Table II-1). Moreover, several of these stages involve complex processes of differentiation and development, and some are known to be susceptible to toxic agents, at least during critical periods. This suggests that exposure of females to toxic agents has the potential to cause more types of adverse effects than exposure of males. However, it does not automatically follow that females are more sensitive to any given agent. The material reviewed later in this report includes more examples of effects from exposure in females than examples of effects from exposure in males, but this may reflect the greater attention that has been paid to maternal exposures during pregnancy (Strobino et al. 1978).

III. SOURCES OF DATA ON REPRODUCTIVE IMPAIRMENT IN HUMAN POPULATIONS

This chapter describes several sets of data on reproductive performance in human populations and discusses their value and limitations for investigating possible effects of external factors, including chemicals. Although extensive data are available on reproductive performance in the human population of the United States, most of the data have been collected as part of routine statistical recording and not for surveillance purposes. Although most of the data sets are not suitable for testing specific hypotheses about effects of external factors, some of them provide useful information about trends and patterns in the frequency of various reproductive outcomes. This chapter pays particular attention to these trends and patterns and to the results of a few extensive research studies.

The available sets of data have been compiled for several different purposes. The largest single body of data--records of vital statistics--is compiled primarily for the registration of births and deaths, and only secondarily for surveillance or research purposes. Other sets of data have been compiled primarily for surveillance of specific outcomes of pregnancy. Some of these data have been used to investigate ethnic differences, geographical patterns, or time trends in the occurrence of various outcomes. They can also provide information on the "background" rate of occurrence of various outcomes in

the human population, and thus can serve as the basis for specific research studies. A few large sets of data have been established specifically for research purposes. In this chapter, we distinguish generally between sets of data collected for statistical, surveillance, and research purposes. However, there is no precise distinction between surveillance and research studies, and both use data from vital statistics and records from hospitals and physicians.

One factor that limits the use of most sets of data for investigating possible effects of external factors is their incompleteness. Not all reproductive impairments and losses that can be measured in humans are recorded or compiled, and the information that is available from vital records, such as birth or death certificates, or from physicians' or hospital records is often inaccurate or incomplete (Lamm 1979, Heuser 1979; see also discussion in Barr et al. 1979). Reproductive failure due to impotence or infertility is not routinely recorded. Losses during the first trimester of pregnancy (spontaneous abortions) are not routinely recorded unless retrospective pregnancy histories are collected. The earliest spontaneous abortions may go completely unnoticed, and other early spontaneous abortions may not be reported to physicians. Thus, most of the early losses and impairments--which are probably substantial, as discussed below--are not recorded.

Losses during the second trimester usually come to the attention of a physician, but despite the requirement by nearly

all states to record fetal deaths of 20 or more weeks' gestation on a fetal death certificate, some may not be recorded (Barr et al. 1979). Fetal losses during the third trimester, including stillbirths, are generally well reported, as are deaths during the neonatal period and during infancy. Congenital malformations are often recorded on birth or fetal death certificates but are not recorded completely or uniformly. Birth weight and length of gestation are uniformly recorded on birth certificates and are routinely compiled. Other types of adverse effects, such as biochemical, behavioral, and immunologic defects, are not easily detected and, if detected, are not systematically reported. Thus, only a few measures of reproductive impairment are available from birth and death certificates, which are the most extensive sources compiled on a national scale. Hospital and physicians' records can also be useful sources of data, but they are expensive to collect and considerations of privacy limit their use for surveillance or research purposes.

Vital Statistics Data

Vital statistics are collected to register, among other events, birth and deaths occurring in the United States. Only limited information is recorded on reproductive outcomes other than births. The National Center for Health Statistics (NCHS) in the Department of Health and Human Services recommends the data that should be collected, but the final form of the certificates is left up to each state. Consequently, there is variation between states in the information recorded in the certificates.

For example, there are several definitions of "fetal losses" that require certification. Most states specify that all fetal losses after 20 weeks of gestation should be reported, whereas some require reporting of all losses. This data source would be far more useful if vital statistics were collected more uniformly over the states both in terms of the items collected and the definitions used; if the certificates included both parents' occupations; and if all fetal losses were certified.

NCHS compiles extensive nationwide data on births (NCHS 1973, 1978a), "prematurity" including low birth weight and shortened gestation (NCHS 1972a, 1980a), congenital anomalies and birth injuries (NCHS 1978c); and infant mortality (NCHS 1972b, 1972c). This information is derived primarily from the states' vital records, and demographic data from the Bureau of the Census have sometimes been linked with vital records by NCHS for the purpose of descriptive studies. Reports and tabulations are published routinely by NCHS, and computer tapes containing detailed and aggregated data are available. Data on congenital anomalies, for example, are classified by age, sex, race, and type of defect, and are often tabulated by county of residence in the United States.

NCHS also conducts periodic surveys of registered births and deaths to complement its ongoing vital statistics programs. In 1972, a National Natality Survey was conducted, and currently (1980) both a National Natality Survey and a National Fetal Mortality Survey are being conducted. These surveys link maternal,

hospital, physician, and other medical sources' records to vital records for the purpose of expanding the information provided on birth and fetal death certificates.

Reporting of some data, such as birth weight, on birth certificates is reliable and complete (NCHS 1980b), but reporting of other data is subject to both under-reporting and incomplete reporting. For example, the data routinely collected on birth defects by NCHS are derived from birth certificates, and only gross abnormalities that are recognized and recorded at birth are covered. In 1973-74, congenital malformations reported on birth certificates constituted 0.8% of live births (NCHS 1978c). In contrast, from the 1972 Natality Survey, congenital malformations recorded in hospitals constituted 4-7% of legitimate, live births.

Several studies have shown that approximately 30-40% of some malformations detectable after 1 year of age are recognized at birth (Myrianthopoulous 1977). The March of Dimes Birth Defects Foundation (1980) estimates that approximately 8% of newborns have birth defects. This estimate is based upon studies of defects that are recognized in the 1st year of life. When both major and minor defects are ascertained through infancy to early childhood, the proportion increases to about 16%, twice that recognized in the 1st year (Chung and Myrianthopoulos 1975). Thus, the NCHS compilation from vital records includes only about 1/10 to 1/20 of the defects that are ultimately detected.

International Surveys of Vital Statistics

Most developed countries have vital records similar to those of the United States, but not all of them compile and analyze the data routinely. Canada, Finland, Sweden, and Norway now have surveillance programs for congenital malformations (Bjerkedal and Bakketeig 1975, Miller and Lowry 1977). The programs in Canada and Norway include extensive monitoring for other reproductive impairments as well. Infant mortality is studied on a much broader scale around the world (NCHS 1967), and low birth weight and prematurity have also been extensively studied (Reed and Stanley 1977). The United Nations and the World Health Organization also have conducted international studies on perinatal mortality that compare rates in different parts of the world (WHO 1978). The United Nations' Statistical Office prepares a Demographic Yearbook based on annual surveys (UN 1977).

The completeness and accuracy of vital statistics vary from one country to another, in part because of differences in the statistical definitions of vital events. As part of the United Nations, the World Health Organization separately publishes a World Health Statistics Annual (WHO 1977). Although the compilation is extensive, with volumes on vital statistics and cause of death, on infectious diseases and cause of death, and on health personnel and establishments, the coverage and the definitions used in different countries are variable. Data are also compiled from hospital records in other countries

as part of the International Fertility Research Project. The data on maternal and infant health are a focus of the project.

Surveillance and Research Studies

A data base on birth defects complementary to that of NCHS is maintained by the Center for Disease Control (CDC) in the Department of Health and Human Services, in cooperation with the National Institute of Child Health and Human Development, the March of Dimes Birth Defects Foundation, and the Commission on Professional and Hospital Activities (CDC 1980). The Birth Defects Monitoring Program (BDMP) of CDC is specifically designed to assess trends over time among major classes of defects, but only in a few areas, such as metropolitan Atlanta, can interviews of parents be conducted.

The data in BDMP are derived from hospital records and consequently are better reported than data based on birth certificates. The overall frequency of birth defects indicated by the data of BDMP is approximately twice that indicated by the NCHS data derived from vital records (See Table III-1). The data are not collected from the entire population, nor from a random sample of the population, but 31.6% of live births in the United States are covered. Because the BDMP is a voluntary program that uses hospital medical records, the data are not generally available outside CDC.

The National Institute of Neurological Diseases and Stroke initiated a National Collaborative Perinatal Project (NCPP) in 1954 to study and prevent perinatal mortality and the "continuum

TABLE III-1

BIRTH DEFECT REPORTING FREQUENCIES--USA, 1974:
COMPARISON OF COVERAGE BY NCHS AND CDC/BDMP

	NCHS*	BDMP+	NCHS/BDMP
Anencephaly	2.1	4.4	47%
Spina bifida	4.5	5.9	77%
Hydrocephalus	1.6	6.1	27%
Cleft Palate	3.0	5.2	57%
Cleft Lip	6.3	9.3	68%
Anorectal Stenosis	1.5	3.4	44%
Down's Syndrome	3.7	8.0	46%

* Vital Statistics Section, NCHS, per 10,000 births.
\+ Congenital Malformation Surveillance Report, CDC, per 10,000 births.

Source: Adapted from Lamm 1979

of reproductive wastage," including congenital malformations, cerebral palsy, mental retardation, deafness, blindness, and disorders of speech. From 1959 to 1965, a total of 55,908 women were registered at 12 institutions, and monitoring of these women and their offspring through age 7 continues to date (USDHEW 1972, Niswander and Drage 1976, Myrianthopoulos and French 1968). Under this program, correlations were sought between 8 categories of malformations and 33 risk variables. Nearly all the variables consisted of diseases and genetic

factors, but cigarette smoking and X-ray exposure were included in the study. Table III-2 contains a summary of the independent and dependent variables investigated. No significant associations were found for X-ray exposure. Cigarette smoking was significantly but negatively correlated with two of the eight dependent variables: "all malformations" and "minor malformations."

A number of data bases have been compiled by states and localities in the United States. Three programs of surveillance of birth defects, in metropolitan Atlanta, Nebraska, and Florida, are conducted in cooperation with BDMP at CDC. In these programs, additional detailed data are collected from mothers and their physicians about potential risk factors. A similar program to obtain information on parents has been conducted by the Boston Collaborative Drug Surveillance Program. At Boston's Lying-In Hospital 15,000 women entering for deliveries since 1977 have been interviewed regarding exposures. There are a number of similar programs in New York and other large cities. For the past 20 years, the Child Health and Development Studies Program of California has collected data on approximately 20,500 pregnancies (Van den Berg 1979). The studies were conducted among members of the Kaiser Foundation Health Plan with the objective of investigating medical, genetic, biological, and environmental factors that influence pregnancy outcome and early development of offspring. The use of a number of drugs during pregnancy has been investigated for associations with

TABLE III-2

EPIDEMIOLOGIC AND GENETIC VARIABLES
USED TO INVESTIGATE CONGENITAL MALFORMATIONS

Independent Variables	Dependent Variables
1. Multiple birth	1. All malformations
2. Maternal age (two categories)	2. Major malformations
3. Prior pregnancy (two categories)	3. Minor malformations
4. Prenatal visits	4. Multiple malformations
5. Socioeconomic index	5. Multiple major malformations
6. Sex of this outcome	6. Anencephaly
7. Fetal death	7. Meningomyelocele meningocele
8. Maternal race	8. Hydrocephaly
9. Maternal inbreeding	
10. Child's inbreeding	
11. Cigarette smoking	
12. Weight gain	
13. X-ray exposure	
14. High blood pressure	
15. Maternal diabetes mellitus	
16. Attenuated live vaccine injection	
17. Viral infection	
18. Bacterial infection	
19. Parasitic infection	
20. Fungal infection	
21. Cardiovascular diseases	
22. Pulmonary diseases	
23. Blood diseases	
24. Metabolic and endocrine diseases	
25. Venereal diseases	
26. Urinary diseases	
27. Gynecologic diseases	
28. Neurologic and psychiatric diseases	
29. Gastrointestinal diseases	
30. Integument diseases	
31. Pregnancy complications	

Source: Adapted from Chung and Myrianthopoulos 1975, Analysis of epidemiologic factors in congenital malformations. In Bergsma, D., ed. Factors Affecting Risks of Congenital Malformations. Symposia Specialists, Miami, Florida, for the National Foundation-March of Dimes, Birth Defects: Original Article Series. Vol. 11, Issue 10, p 5

adverse fetal effects. Cigarette smoking has also been investigated. Los Angeles County conducts studies of vital statistics (L.A. 1977), and most states and large cities have similar programs utilizing vital statistics to search for potential problems.

An end point of particular concern for which there is very limited information is infertility. Although the NCHS devotes considerable attention to fertility and its distribution and determinants (NCHS 1977a, 1978b), much of the information analyzed is on fecundity. Only recently have infertility and reproductive impairments been the subject of a broad survey. An improved surveillance system could include data on unsuccessful attempts at pregnancy and spontaneous abortions, in addition to data on the end points now compiled and evaluated.

Other Potentially Useful Types of Data

Existing programs to compile and analyze data for the purpose of surveillance rely primarily upon vital statistical data and to some extent on hospital records for birth defects. Generally, the only environmental hazards that will be detected from this information are those for which there is an overwhelmingly strong association with one factor and to which a substantial number of people are exposed. In some cases, hazards are evident because of the extreme distinctiveness of the effect produced. Even then, a potential hazard may not be easily detected. For example, Sweden had a national scheme for monitoring rare malformations covering 20,000-40,000 births per

year when the thalidomide epidemic occurred (Weatherall and Haskey 1976). The increases in limb malformations were not recognized during that period but, in retrospect, were recognizable if the data had been properly analyzed.

Improvements in the completeness and accuracy of the data now compiled are likely to strengthen these programs. However, other types of information may prove to be more sensitive indicators of reproductive hazards, particularly if they cover the early periods in reproduction when substantial losses and damage occur.

Kline et al. (1977b) recommended that the incidence of spontaneous abortions and the prevalence of defects in aborted fetuses are advantageous and sensitive end points for surveillance of potential teratogens. Spontaneously aborted fetuses can be studied in detail and preserved for future study, and the range of anomalies seen in aborted fetuses is greater than that seen in live births.

A number of other types of information that may prove to be sensitive indicators of reproductive impairments are, in essence, measures of performance and behavior of offspring (see discussion in Barr et al. 1979). These include, among many others:

1. Apgar score, which is computed 1 and 5 minutes after birth and includes heart rate, respiratory effort, muscle tone, and reflex irritability

2. Prechtl neurologic exam, which is an elaborate neurologic evaluation of newborn infants

3. Brazelton neonatal behavioral assessment, which includes a series of neurologic and behavioral measures of an infant's response to environmental stimuli

4. Bayley scale, which is a measure of gross motor, fine motor, language, and social functioning in infants and is comparable to an IQ scale

5. Stanford-Binet IQ scale and its derivatives, which are applicable to older children

When combined with measures of fetal growth and development, such as birth weight and prematurity, some of these measures might be used for surveillance. Apgar scores are now widely recorded at birth and provide a crude overall measure of infant viability.

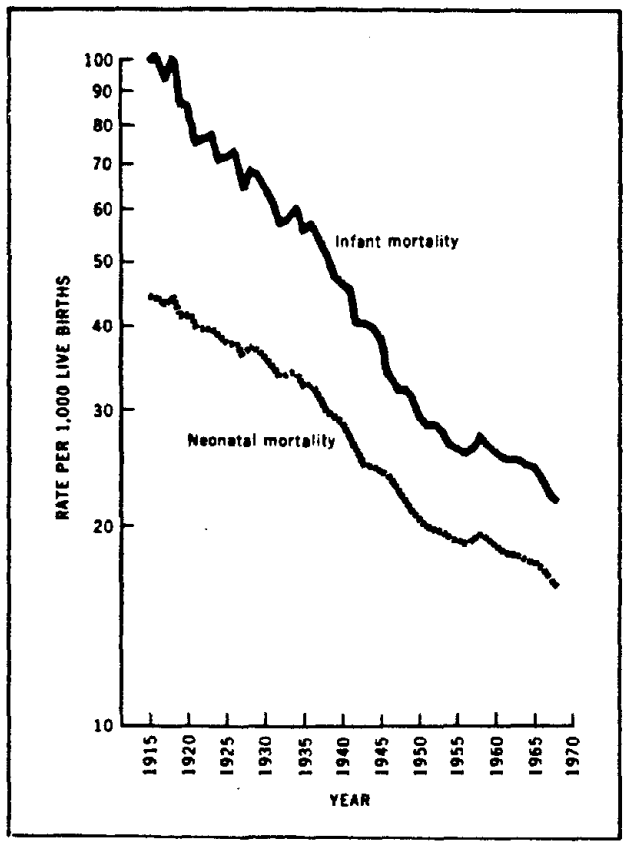
In addition to end points that should be monitored, efforts to link data systems to facilitate the study of associations between adverse reproductive effects (and other diseases) and chemicals may prove worthwhile. This subject has been addressed by NCHS in compliance with P.L. 95-623, the Health Services Research, Health Statistics, and Health Care Technology Act of 1978 (NCHS 1977b, 1980d).

Trends and Patterns

Trends in infant mortality have been widely studied. A significant decline in infant mortality has taken place in the United States since 1900 (Figure III-1) and has also occurred in most developed countries (Weatherall and Haskey 1976). The proportion of infant deaths that occur in the neonatal period (up to 4 weeks after birth) has risen steadily, while the actual rate of neonatal deaths has declined. This probably

FIGURE III-1

INFANT AND NEONATAL MORTALITY RATES:
UNITED STATES, 1915-68



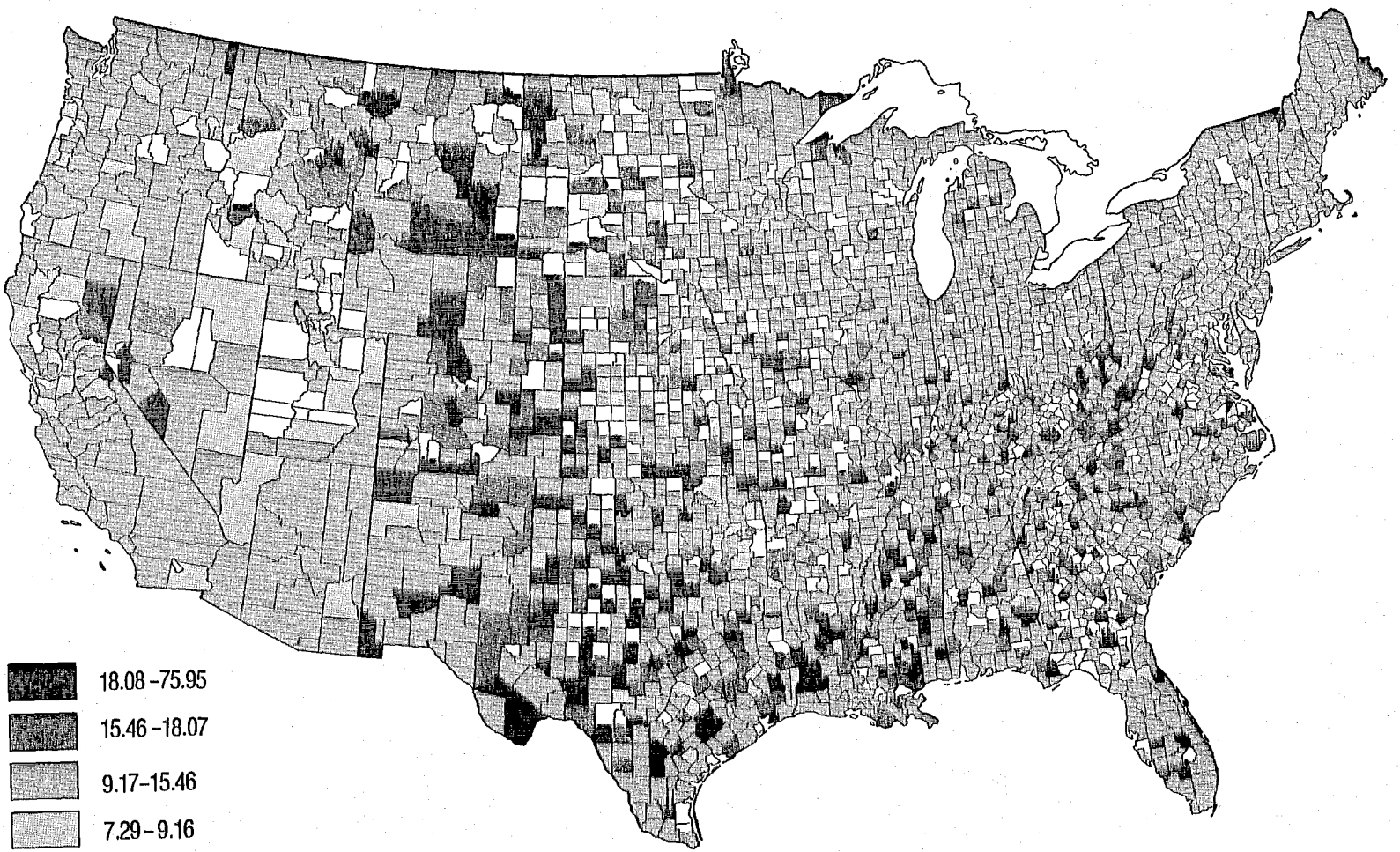
Source: NCHS 1972c

reflects improved neonatal care in many areas of the country, which would tend to decrease both neonatal and total infant deaths but have less impact on earlier than on later deaths.

The geographical distribution of infant mortality in the United States has been mapped by Keller and White (1980), who used statistics collected county by county. Figures III-2

FIGURE III-2

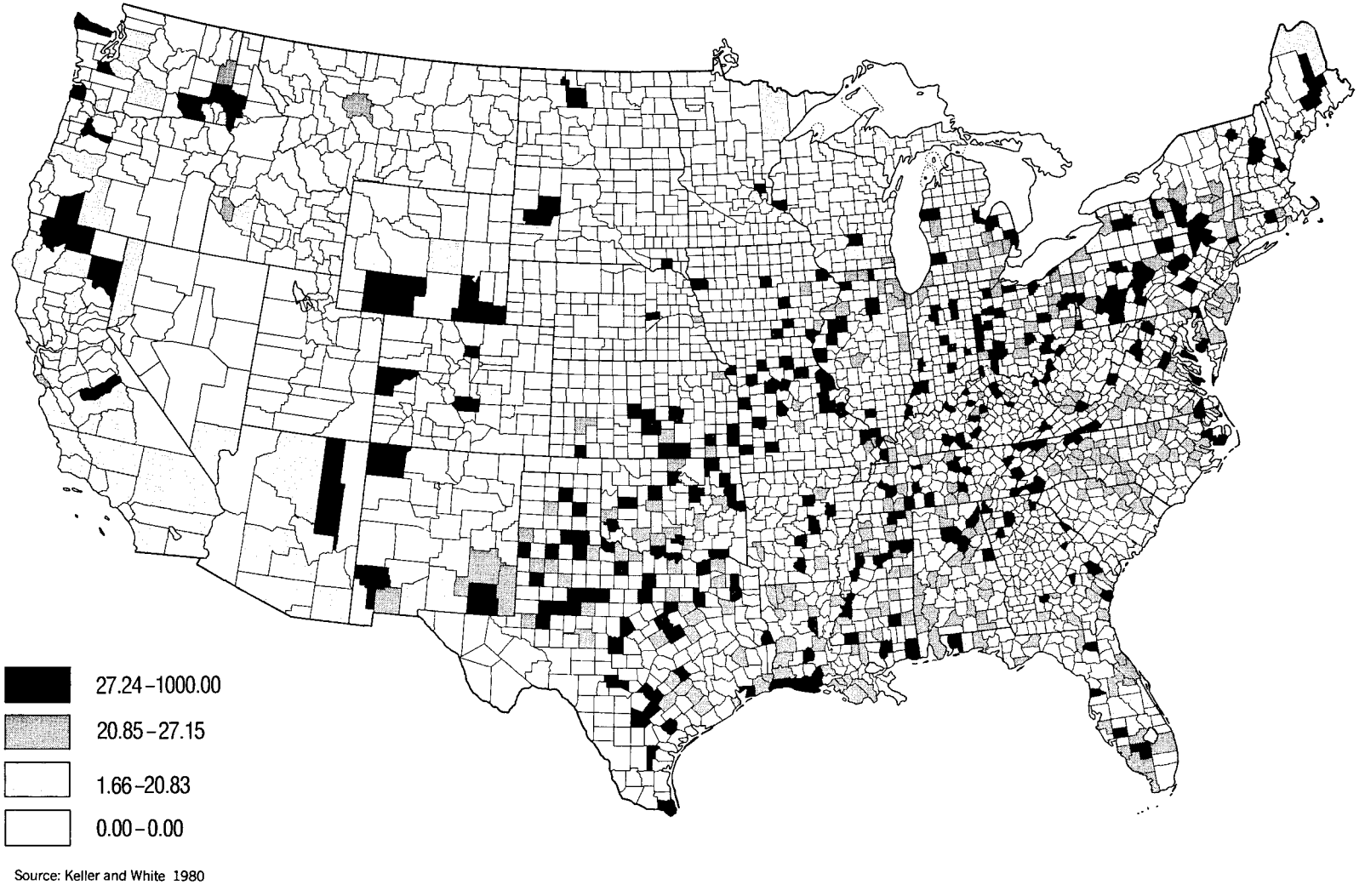
INFANT MORTALITY RATES FOR WHITES DURING THE FIRST SIX DAYS AFTER BIRTH, 1969-1974 RATE PER 1,000 LIVE BIRTHS



Source: Keller and White 1980

FIGURE III-3

INFANT MORTALITY RATES FOR BLACKS DURING THE FIRST SIX DAYS AFTER BIRTH, 1969-1974 RATE PER 1,000 LIVE BIRTHS



Source: Keller and White 1980

and III-3 show markedly different patterns of deaths within the 1st week after birth in whites and blacks. These data suggest that factors associated with race, such as lifestyle, economic status, and medical care, may influence early neonatal mortality. The geographical patterns for late neonatal deaths (7 days to 1 year after birth) are markedly different, suggesting that different factors are involved.

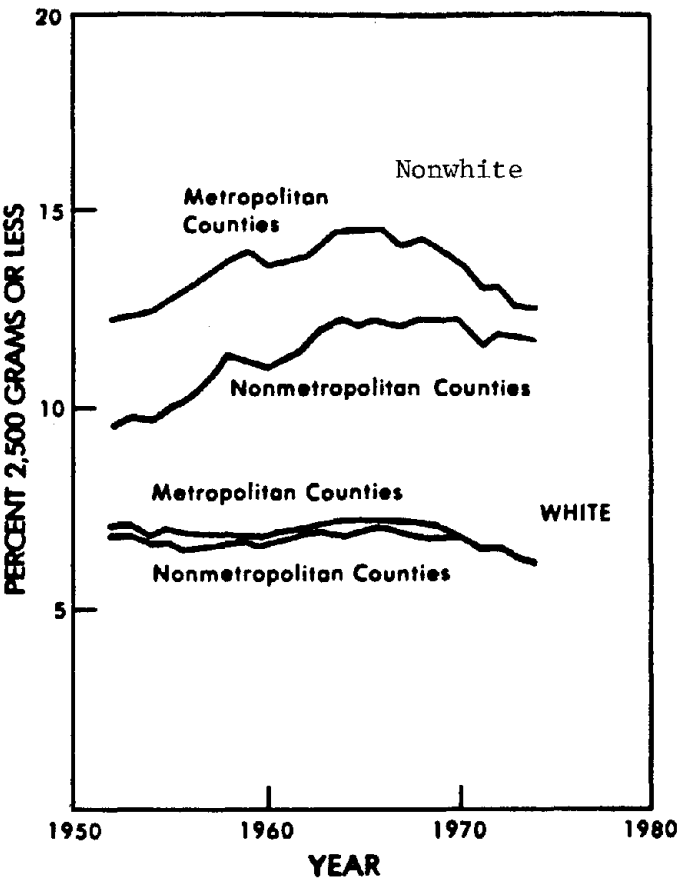
Prematurity and low birth weight have also been extensively studied (Pratt et al. 1977). In the United States, the proportion of infants with low birth weight (less than 2.5 kg) among live births increased from 7.7% in 1960 to a peak of 8.3% in 1965 and 1966, and declined in 1978 to 7.1% (NCHS 1980a). Figure III-4 shows that most of this peak occurred in nonwhites and that the frequency of low birth weights was somewhat higher in urban areas than in rural areas.

Maps of the geographic distribution of the frequency of low birth weights show marked geographic patterns, somewhat similar to those of neonatal mortality shown in Figures III-2 and III-3 (Chase 1977).

Some geographic variation is evident in the data collected by CDC on congenital malformations over the past 8 years. Trends over time in individual types of malformation are mixed, with some steady, some declining, and others increasing (CDC 1980). Figure III-5 shows marked increasing trends in ventricular septal defects and patent ductus arteriosus, and a marked decreasing trend in anencephaly. A dramatic illustration of a temporal

FIGURE III-4

LOW BIRTH WEIGHT RATIOS AMONG LIVE BIRTHS BY GEOGRAPHIC CLASSIFICATION AND COLOR: UNITED STATES, 1952-74



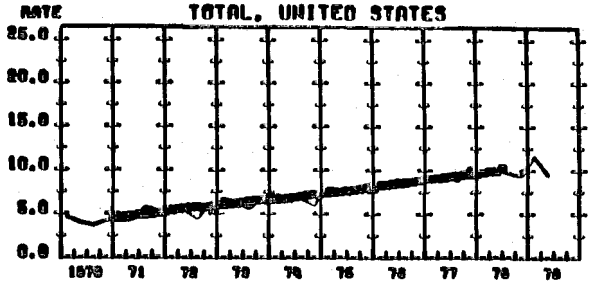
Source: Adapted from Chase 1977, Time trends in low birth weight in the United States, 1950-1974. In Reed, D.M., and Stanley, F.J., eds. The Epidemiology of Prematurity. Urban and Schwarzenberg, Baltimore. Figure 1, p 24

change in malformation rate is provided by the data on occurrence of anencephaly and spina bifida in New England and New York from 1900-1971 (Figure III-6). This trend was originally observed in a Boston hospital (MacMahon and Yen 1971). Both of these

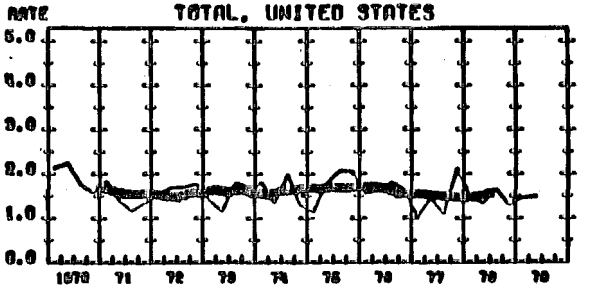
FIGURE III-5 TRENDS IN REPORTED PREVALENCE, BY QUARTER OF BIRTH, BY U.S. CENSUS REGION, JANUARY 1970-JUNE 1979

Birth Defects Monitoring Program (rates per 10,000 total births)

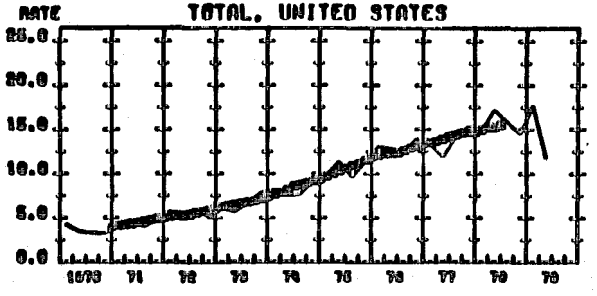
VENTRICULAR SEPTAL DEFECT



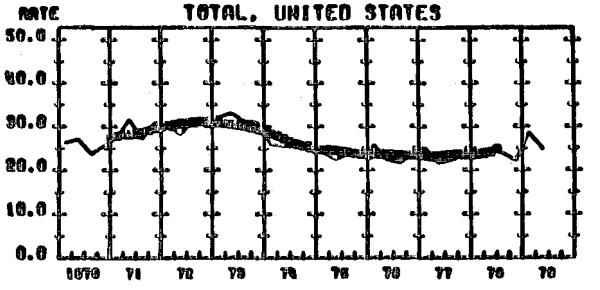
TRACHEO-ESOPHAGEAL FISTULA



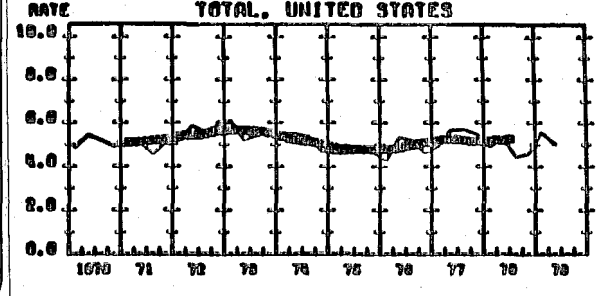
PATENT DUCTUS ARTERIOSUS



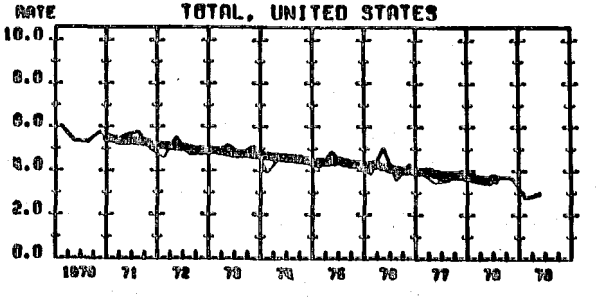
CLUBFOOT W/OUT CNS ANOMALIES



CLEFT PALATE W/OUT CLEFT LIP



ANENCEPHALY



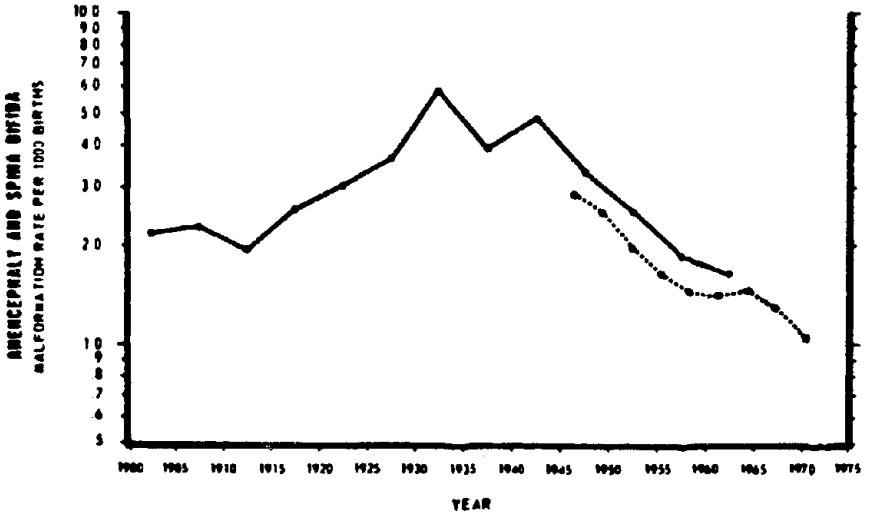
——— Quarterly Rates

▪▪▪▪▪▪▪▪▪▪ 2-Year Moving Average

Source: CDC 1980

FIGURE III-6

PREVALENCE OF ANENCEPHALY AND SPINA BIFIDA
IN SECTIONS OF THE NORTHEASTERN UNITED STATES
FROM 1900-1971 (-) NEW ENGLAND, (---) NEW YORK



Source: Janerich 1973, Epidemic waves in the prevalence of anencephaly and spina bifida in New York state, Teratology 8:253 (Copyright by the Wistar Institute Press, Philadelphia)

malformations of the central nervous system (CNS) are readily recognizable and are less likely than many other malformations to be missed or misdiagnosed. Table III-3 shows marked geographical variations in both the rate of CNS malformations and the proportion of CNS malformations among all reported malformations. These data may reflect different degrees of diagnosis and reporting, but they suggest that there may be considerable geographical variation in countries around the world and possibly within the United States as well.

TABLE III-3

PREVALENCE OF CONGENITAL MALFORMATIONS OF THE CENTRAL NERVOUS SYSTEM IN VARIOUS STUDIES

Investigator	City or country	No. of births	No. with any malformation	No. with CNS malformations	Rate of CNS malformations per 10,000	Proportion (%) of CNS malformations among all malformations
McIntosh et al, 1954	New York, USA	6,053	433	67	110.69	15.47
Neel, 1958	Japan	64,569	863	95	14.71	11.01
Saldanha, 1964	São Paolo, Brazil	22,781	739	60	26.34	8.11
Stevenson et al, 1966	Worldwide	416,695	5,290	1,495	35.88	28.26
Nelson and Forfar, 1969	Edinburgh, UK	8,648	470	81	93.27	17.23
Newcombe, 1969	Nova Scotia, Canada	18,314	654	76	41.50	11.62
Woolf and Turner, 1969	Salt Lake City, USA	59,561	1,227	129	21.99	10.68
Villumsen, 1970	Copenhagen, Denmark	9,182	350	45	49.01	12.86
Myrianthopoulos and Chung, 1974, 1975						
major and minor malformations	USA	54,454	8,507	577	105.96	6.78
major malformations only			4,457	453	83.19	10.16
Saxén et al, 1974	Finland	721,092	9,178	1,010	14.00	10.98
Weatherall (personal communication)	England and Wales	3,814,205	84,640	15,545	40.76	22.16

Source: Myrianthopoulos 1979, Our load of central nervous system malformations. In Myrianthopoulos, N.C., and Bergsma, D., eds. Recent Advances in the Developmental Biology of Central Nervous System Malformations. Alan R. Liss, New York, for the National Foundation-March of Dimes, Birth Defects: Original Article Series. Vol. 15, Issue 3, pp 1-18

No systematic study of the geographical variation in the rates of congenital malformations in the United States has been undertaken. A limited analysis of the overall rates of malformations using data from NCHS (1978c) over the period 1973-1975 (aggregated to reduce some of the statistical variation in rare events) has been conducted for this report. This analysis shows that the variation between states is considerable; when broken down by county, the variation is even greater. Table III-4 lists the rates of congenital anomalies for each state in 1974. The highest rate in any state (New Mexico) was approximately 4.5 times the lowest rate in any state (Maryland). Some of this difference may be due to reporting differences or to random variation, but environmental factors may also be important. In New Mexico, one county (San Juan) showed high rates in each year from 1973 to 1975; the average rate was about 28 times higher than that in another county (Dona Ana) during the same period. Both counties have populations of similar size, and only part of this variation is likely to be due to reporting differences or random variation. In other counties, however, there were marked variations from year to year. For this reason, Heuser (1979) suggested that it may be difficult to use these data to study associations with specific agents or factors.

The interpretation of existing data is complicated by several biasing factors resulting from differences in diagnosis and reporting and by possible statistical variations. However,

TABLE III-4

RATE OF CONGENITAL ANOMALIES PER 100,000 LIVE BIRTHS IN THE UNITED STATES DURING 1974 AS REPORTED FOR EACH OF 46 STATES AND THE DISTRICT OF COLUMBIA

State	Rate of Anomalies	State	Rate of Anomalies
Alabama	560	Montana	870
Alaska	880	Nebraska	960
Arizona	1,000	Nevada	1,200
Arkansas	710	New Hampshire	800
California	800	New Jersey	NR
Colorado	970	New Mexico	1,900
Connecticut	690	New York	720
Delaware	510	North Carolina	NR
D.C.	380	North Dakota	1,200
Florida	730	Ohio	980
Georgia	NR	Oklahoma	740
Hawaii	990	Oregon	900
Idaho	730	Pennsylvania	730
Illinois	980	Rhode Island	540
Iowa	1,100	South Carolina	600
Kansas	520	South Dakota	1,500
Kentucky	710	Tennessee	530
Louisiana	590	Texas	620
Maine	907	Utah	820
Maryland	420	Vermont	910
Massachusetts	940	Virginia	740
Michigan	960	Washington	1,200
Minnesota	1,000	West Virginia	910
Missouri	880	Wyoming	1,200

NR: Not reported

Source: Adapted from NCHS 1978d

the data reviewed above suggest that geographical and temporal differences in reproductive impairment may nevertheless be large enough to be useful in generating hypotheses. By themselves, the patterns do not indicate specific etiological factors or agents; further study and evaluation are needed to formulate and test specific hypotheses. In particular, these geographical patterns have not been used to generate hypotheses about chemical agents that may contribute to the observed effects. The existence of clear trends and patterns, if reliably established through additional investigation, would serve to define better the importance of environmental factors, including chemicals.

The Extent of Reproductive Impairment in the United States

The data sources described in this chapter have provided information on the prevalence of certain types of reproductive impairment in the United States. An estimated 6,954,000 married couples in the United States are infertile, 3,000,000 of whom have at least one partner who is noncontraceptively sterile (Mosher 1980, Placek and Cynamon 1980). Although spontaneous abortions often go unreported, particularly among pregnancies of less than 20 weeks of gestation, they have been estimated to occur at a frequency of 15% of all recognized pregnancies (Warburton and Fraser 1964). This figure is generally considered to be an underestimate of the true rate, insofar as most spontaneous abortions occur early in gestation, often before the pregnancy is recognized. Of approximately 3 million live births a year, 13.1 per 1,000 terminate in infant death within the

1st year (NCHS 1980a). One in twelve (8.3%) of infants born alive have congenital malformations recognized within the 1st year of birth (March of Dimes Birth Defects Foundation 1980). When defects that become apparent only later in life are included, the frequency of major and minor malformations increases to about 16% (Chung and Myrianthopoulous 1975). Approximately 7% of babies are born prematurely (before the 37th week of gestation), and 7% of infants born at full term have low birth weights (2.5 kg or less) (USDHEW 1972).

It is difficult to estimate the overall rate of reproductive impairment in the human population, both because the figures quoted above for specific types of impairment are incomplete and nonexclusive and because figures for early losses are scanty. Roberts and Lowe (1975) estimated that 78% of fertilized ova in England and Wales were lost before birth. Schlesselman (1979), using a different method, estimated that 16% of ova subject to fertilization were not fertilized and a further 53% were fertilized but did not give rise to live births (total loss of 69% through birth). However, Schlesselman's estimates for early losses were based on two small samples of embryos. Stickle (1968) estimated that 32% of all conceptions result in spontaneous abortion, stillbirth, or infant death, but did not attempt to include very early losses. Oakley (1978) estimated 25% losses after the 4th week of pregnancy. The differences between estimates reflect primarily the large uncertainty in the frequency of very early losses. The estimates of losses

cited above, which range from 32% to more than 78%, do not include all types of impairment. The higher figure, for example, does not include prematurity, low birth weight, or birth defects.

At present, it is not possible to separate the proportion of reproductive impairments due to spontaneous occurrence from that due to external factors.

Human disease states in general result from an interaction between external insult and genetic susceptibility. The importance of the genetic component in reproductive dysfunction has been illustrated in a study of genetically identical, monozygotic twins (Myrianthopolous 1975). An increased frequency of malformations was found in identical twins compared to nonidentical (dizygotic) twins or singletons. However, among the 34% of identical twins that had malformations, one-third had different malformations. Genetic susceptibility alone does not determine the level or type of malformation.

Wilson (1973a) has estimated that 23-35% of birth defects have an identified genetic component (including chromosomal aberrations) and 7-11% have an identified environmental factor, including radiation, drugs, environmental chemicals, infections, and maternal metabolic imbalances. He estimated that, for 65-70% of defects, no causative factors have been identified. No comparable estimates are available for reproductve impairments other than birth defects.

IV. DRUGS AND OTHER CHEMICALS REPORTED TO AFFECT REPRODUCTIVE FUNCTION IN HUMANS

Despite the limited nature and availability of population-based data on adverse reproductive effects and the difficulty of obtaining reliable exposure data, a number of different chemical agents have been associated convincingly with various types of reproductive effects in humans. The identification of such associations generally depends on the existence and accessibility of well-defined groups within the population with reasonably well-characterized exposure to the agent under consideration. Some examples are: workers highly exposed in the workplace to one or a limited number of chemicals; patients treated by physicians with specific drugs; or, in a few cases, segments of the general population unusually and highly exposed to environmental chemicals.

Epidemiological Considerations

Four types of study provide evidence in humans for an association between exposure to a chemical and an adverse reproductive effect:

1. Case reports
2. Ecologic studies
3. Case-control studies
4. Cohort studies

The last two types of study generally provide more convincing evidence for an association than the first two, because they

are better controlled. However, the first two types of study can at least generate hypotheses about associations, and in some cases they may provide strong evidence for the validity of such hypotheses.

1. Case reports. Case reports have often served as the initial basis for implicating specific compounds, although the hypotheses generated from these reports are generally tested systematically in controlled studies before they are regarded as conclusive. In some instances when the effect is both pronounced and specific, such observations may provide strong evidence for an association between a substance and the outcome observed. For example, the conclusions that folate antagonists increase the risk of spontaneous abortions and that tetracycline leads to miscalcification are based on case reports. Clusters of affected individuals have usually been noted by clinicians. However, more recently groups of affected individuals have themselves noted common adverse effects and ventured to ascribe their problem to a specific exposure (e.g., DBCP and 2,4,5-T). When epidemiologic studies have been launched to test these observations, the results of such studies have sometimes been confirmatory (e.g., DBCP), sometimes controversial (e.g., 2,4,5-T).*

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*In the case of Love Canal, reports of an increased frequency of spontaneous abortions and birth defects among local residents have been widely publicized, but no systematic study of pregnancy outcome has yet been published. In the case of the incident at Seveso, Italy, reports of adverse effects have similarly appeared in the news media, but studies reported in the scientific literature have not been sufficiently systematic to draw conclusions.

2. Ecologic studies. Ecologic studies generally attempt to relate group differences in exposure to group differences in the frequency of various adverse effects. Uses of this approach can be found in the literature discussed below. For example, one study compared rates of central nervous system malformations in communities with and without vinyl chloride plants (Infante et al. 1976b). Ecologic studies generally use data that are readily available and thus may serve as quick, preliminary tests of an hypothesis; such studies often provide a basis from which to decide whether to initiate more intensive studies.

Ecologic studies have the disadvantage, however, of being so subject to the influence of misclassifications and confounding factors that results may underestimate, overestimate, or even reverse the direction of the relationship between exposure and outcome at the individual level (Robinson 1950). Findings from ecologic studies, therefore, are often viewed as tentative, awaiting confirmation in studies of individuals for whom the fact of exposure or disease can be confirmed and account can be taken of potentially confounding variables. Such factors as age, race, cigarette smoking, and alcohol use can be confounding variables and may relate both to the hypothesized exposure and the observed effects in these studies.

Table IV-1 sets out for several common reproductive impairments some potentially confounding variables that can complicate the interpretation of data from ecologic studies on associations

between the chemical or other study factors and the measured outcome.

TABLE IV-1

POTENTIALLY CONFOUNDING FACTORS FOR
A NUMBER OF ADVERSE REPRODUCTIVE EFFECTS

Adverse Reproductive Effects	Potentially Confounding Factors
Impaired spermatogenesis	Surgical procedures such as vasectomy; diseases and illnesses such as varicocele, fever, mumps, and diabetes; certain therapeutic drugs
Reduced fertility	Contraceptive use
Spontaneous abortion	Maternal age, cigarette smoking, alcohol consumption, history of spontaneous abortions
Low birth weight	Race, cigarette smoking, parity, maternal nutrition
Birth defects: e.g,	
Down's syndrome	Maternal age
Neural tube defects	Ethnic factors

3. Case-control studies. Controlled epidemiologic studies fall into two broad classes depending on whether the initial basis for study is a group of people with an identified disease or impairment (cases) or a group exposed to a chemical or other risk factor (a cohort) (Mausner and Bahn 1974, MacMahon and Pugh 1970). Case-control studies compare the frequency of

exposure to the hypothesized causal factor in persons with the disease or impairment and persons without disease but otherwise comparable with respect to important confounding variables.

The case-control approach is particularly useful when the outcome under study is relatively rare. If the outcome occurs frequently in the general population, this approach is likely to provide useful evidence only on factors to which there is widespread exposure or which have a relatively strong influence on the outcome.

4. Cohort studies. In this type of study, comparison groups differ in their exposure to the substance or factor under study; they may be unexposed or exposed to a distinctly different degree; occasionally, the comparison group may be the general population for which prevailing rates of the impairments under study are known. As in ecologic and case-control studies, the appropriate confounding variables need to be considered.

The cohort approach is often used when the exposure under study is infrequent relative to the outcome of concern. When such factors as smoking or alcohol use are being studied, large cohorts can be readily identified. However, many groups exposed in the workplace or community consist of small numbers of individuals, and the size of the cohort can then limit the probability of detecting associations that may exist (i.e., low statistical power). With small cohorts and relatively infrequent outcomes,

the statistical power of studies to detect modest associations is small, making interpretation of negative findings difficult.

Interpretation of Study Findings

Because of the limitations inherent in any study of human populations, findings from a single study of any type are rarely accepted as conclusive evidence unless they show distinctive, large, or otherwise conspicuous effects. Epidemiologic findings become more convincing when the results of independent studies conducted on the same substance under different circumstances are consistent. In evaluating an epidemiologic study, the findings are often considered in light of how much is confirmed by other studies.

In any of these studies, a number of important and complex considerations enter into the evaluation of the study findings. The difficulty of determining the presence or absence of the impairment under study, the fact and degree of exposure to a chemical, and the existence of confounding factors that may affect the end point or exposure are perennial problems. Human disease and illness involve many different contributory factors, and people are exposed to a variety of chemicals and other potentially contributory factors throughout life.

Reviews of the Existing Studies

Unfortunately, few chemicals have been thoroughly studied. Even the substances that have been examined in several studies cannot be said to be comprehensively investigated, because

only one, or at best a few, of the numerous reproductive end points has been considered. Furthermore, the effects of exposure have usually been assessed in only one of the parents, or maternal and paternal exposures have not been differentiated. Exposures before conception and during pregnancy are often analyzed together, and it is difficult in such studies to know with any precision what hypothesis is being tested.

Existing studies indicate that the timing of exposures to chemicals in the lives of parents may determine the type of adverse outcome. In their review, Strobino et al. (1978) cited the example of oral anticoagulants. When administered to women early in pregnancy, there was increased risk of nasal and skeletal anomalies in their offspring; when administered in late pregnancy, these drugs were associated with an increased risk of fetal hemorrhage and stillbirth. Chromosomal abnormalities in the fetus probably result from exposures that occur either before conception or around the time of fertilization and implantation; other outcomes, such as congenital malformations, are likely to result from exposures that occur during a specific time in organogenesis; still other outcomes, such as intrauterine growth retardation, probably result from exposures during pregnancy (although limited observations in humans and mice raise the possibility of mechanisms that operate before conception: Pharoah et al. 1977).

Sources of Data on Chemical Hazards to Human Reproduction

Several reviews have been published on various aspects of human reproductive impairment from chemicals. Strobino

et al. (1978) reviewed data on adverse effects of a number of drugs, cigarette smoking, alcohol consumption, and a few other chemicals. They tabulated data on nine different end points ranging from spontaneous abortions to cancer and childhood mortality; the reported effects were classified according to paternal and maternal exposure, and the latter was further subdivided by timing of exposure in relation to pregnancy. Schardein (1976) reviewed the literature on teratogenic effects of drugs. Wilson (1973a, 1977, Wilson and Fraser 1977a) and Shepard (1980) compiled data on other teratogenic agents. Hunt (1979) reviewed factors in the workplace, including toxic chemicals, that affect the reproduction and health of male and female workers, although the report was focused on women in the workforce. Sullivan and Barlow (1979) surveyed the literature on teratogenic and other reproductive effects of chemicals in the general environment and in the workplace.

In this chapter, data from these and other sources have been used to compile lists of chemicals known or suspected to cause adverse effects on human reproduction. To illustrate the nature of the evidence for the effects listed in this chapter, summaries of the scientific literature on selected chemicals are presented in Appendix A, listing evidence in both humans and animals for a range of chemicals. The evidence in humans for adverse effects is of variable quality and is often incomplete or inconclusive. Although a few thorough, well-controlled, epidemiological studies have been conducted, the available

evidence for most chemicals is limited to case reports or retrospective surveys of relatively small groups of exposed people. The studies summarized in Appendix A on chemicals associated with human reproductive impairment also demonstrate the difficulties encountered in enumerating the affected individuals, in selecting appropriate control groups, and in documenting exposure.

The remainder of this chapter is divided into seven sections, according to the manner in which humans are exposed to the types of chemicals under consideration:

1. Therapeutic drugs
2. Cigarette smoking
3. Alcohol consumption
4. Illicit and addictive drugs
5. Workplace hazards
6. Environmental chemicals and food contaminants

Three other classes of chemicals to which humans are widely exposed are cosmetics, food additives, and consumer products. These classes of chemicals are not discussed in this chapter because they have rarely, if ever, been studied for reproductive effects, and we have found no significant literature on them.

1. Therapeutic drugs

a. Teratogenic effects. Teratogenic effects of therapeutic drugs have been reviewed by Strobino et al. (1978), Schardein (1976), and Wilson (1977). Table IV-2 lists the five classes of drugs recognized by Schardein as teratogenic in humans,

TABLE IV-2

THERAPEUTIC DRUGS KNOWN TO BE TERATOGENIC IN HUMANS

Drug	Effects	Number of cases known
Thalidomide	Malformations of limbs (phocomelia) and ears	7,000-8,000
Androgenic hormones[a]	Virilization of females	37
Progestogens[b]	Virilization of females	>600
Folate antagonists[c]	Multiple malformations	12
Antithyroid drugs[d]	Goiter, hypothyroidism, mental retardation	>100
Diethylstilbestrol[e]	Vaginal adenosis and clear cell adenocarcinoma in females; various genital defects in males and females, menstrual disorders	2,000-3,000 (estimated to be at least 400,000-600,000 with some abnormality)[f]

[a]Testosterone, methylandrostenediol, methyltestosterone, 19-nortestosterone

[b]Progesterone, allylestrenol, chlormadinone, ethisterone, medroxyprogesterone, norethindrone

[c]Aminopterin, methotrexate

[d]Iodides, thiouracil, propylthiouracil, and imidazols

[e]Not listed as a teratogen by Schardein: See IARC 1979

[f]See Herbst 1976 and USDHHS 1980

Source: Adapted from Schardein 1976, Drugs as Teratogens. CRC Press, Boca Raton, Florida. P 6 (Copyright The Chemical Rubber Co., CRC Press, Inc.)

together with diethylstilbestrol (DES). Table IV-3 lists a number of other drugs and classes of drugs categorized by Wilson (1977) as "suspected of embryotoxicity in man" or "possibly embryotoxic in man." As shown in Appendix A, the data for several of these drugs (methotrexate, warfarin, and busulfan) are limited and are based primarily on a small number of case reports. Wilson (1977) concluded that these drugs are "mildly embryotoxic under certain infrequent conditions," so that the associations become apparent only in large numbers of cases or in epidemiologic studies.

Evidence is conflicting for an association between birth defects and maternal exposure to stimulators of ovulation, hormones, and pregnancy tests used around the time of conception. An effect, if present, is likely to be due to exposure after conception rather than exposure before conception (Strobino et al. 1978). Schardein (1976) listed a number of drugs as possible teratogens, citing reviews by Wilson (1973a), Catz and Abuelo (1974), and Tuchmann-Duplessis (1965). The suspect drugs include trimethoprim-sulfisoxazole, barbiturates, aspirin, certain antacids, nicotinamide, iron, certain antihistamines, dicumarol, excess amounts of vitamins A and D, chloroquin, LSD, quinacrine, phenylbutazone, promethazine, pyrimethamine, mercaptopurine, cyclophosphamide, chlorambucil, meclizine, certain sulfonamides, trifluoperazine, phenmetrazine, cortisone, podophyllotoxin, serotonin, and tetracycline (Schardein 1976).

TABLE IV-3

THERAPEUTIC DRUGS SUSPECTED TO BE TERATOGENIC IN HUMANS

Type of Drug and Specific Examples	Types of Defect
Anticonvulsants Diphenylhydantoin Trimethadione	Facial, digital, cardiac, mental
Neurotropic-anorectics Amphetamines	Cardiac and various
Oral anticoagulants Coumarin (warfarin)	Nasal, optic, mental, skeletal
Alkylating agents Busulfan	Intrauterine death, few defects
Oral hypoglycemics Tolbutamide Other sulfonylureas	No definable syndrome
Tranquilizers Chlordiazepoxide Meprobromate Diazepam	No general pattern
Salicylates Aspirin	No syndrome
Antibiotics Tetracycline Streptomycin	No syndrome
Antituberculosis agents	Various
Antimalarials Quinine	Abortion, deafness
Lithium carbonate	Skeletal, cardiac, death

Source: Adapted from Strobino et al. 1978, Wilson 1977a, and Schardein 1976

b. Nonteratogenic effects. Although several of the drugs (e.g., folate antagonists, alkylating agents) listed in Tables IV-2 and IV-3 induce spontaneous abortions as well as congenital malformations, there appears to be no comprehensive survey of drugs that cause adverse effects other than teratogenicity. Epidemiologic studies examining the effects of drugs have focused, for the most part, on exposures to the mother either during pregnancy or before conception. Table IV-4 lists some 40 drugs or classes of drugs for which nonteratogenic adverse effects on the human fetus have been reported. Strobino et al. (1978) listed 16 studies of reproductive outcomes in women who took oral contraceptives before conception. These studies have given generally negative results for a number of end points, although there is some evidence to indicate a decreased risk of spontaneous abortion (Alberman et al. 1976, Rothman 1977, Stein and Susser 1978). Strobino et al. (1978) summarized adverse side effects of several drugs on male and female fertility, but possible effects on other reproductive functions such as endocrine function or libido, have not been reviewed.

Tables IV-2 to IV-4 together show that a wide variety of drugs has been shown to have teratogenic or other adverse effects on the human fetus after maternal administration. This is not surprising in view of the fact that drugs are administered in therapeutic doses (i.e., in doses intended to affect physiological or other functions of the mother). In principle, the requirements for clinical trials of new drugs and for reporting

TABLE IV-4

NONTERATOGENIC ADVERSE EFFECTS OF DRUGS ON THE HUMAN FETUS

Maternal Medication	Fetal/Neonatal Effect
Salicylates, large amounts	Bleeding
Tetracyclines	Deposition in bone; inhibition of bone growth in premature infants; discoloration of teeth
Iodophenoxic acid	Elevation of serum PBI
Chloroquin	Death(?)
Coumarin anticoagulants	Hemorrhage, death
Chlordiazepoxide	Withdrawal syndrome(?)
Sulfonamides	Kernicterus(?); anemia(?)
Diazepam	Hypothermia
Tolbutamide	Thrombocytopenia
Meperidine	Neonatal depression
Magnesium sulfate	Central depression and neuromuscular block
Chloramphenicol	Death("gray syndrome")
Novobiocin	Hyperbilirubinemia(?)
Alphaprodine	Platelet dysfunction
Thiazide diuretics	Thrombocytopenia; salt and water depletion; neonatal death(?)
Erythromycin	Liver damage(?)
Lithium	Cyanosis and flaccidity
Nitrofurantoin	Hemolysis
Primidone	Withdrawal syndrome(?)
Primaquine, pentaquine	Hemolysis(?)
Vitamin K analogs, excess	Hyperbilirubinemia
Ammonium chloride	Acidosis
Adrenocortical hormones	Adrenocortical suppression
Prednisolone	Acute fetal distress;fetal death(?)
Reserpine	Nasal congestion; lethargy; respiratory depression; brachycardia

TABLE IV-4 (continued)

Maternal Medication	Fetal/Neonatal Effect
Quinine	Thrombocytopenia
Sedatives	Behavioral changes
Hexamethonium bromide	Neonatal ileus
Intravenous fluids, excess	Fluid and electrolyte abnormalities
Barbiturates, diphenylhydantoin	Coagulation defects; with drawal syndrome (barbiturates only)
Phenobarbital, excess	Neonatal bleeding; death
Chlorpropamide	Prolonged hypoglycemia
Phenformin	Lactic acidosis(?)
Mepivacaine	Fetal brachycardia and depression
Meprobamate	Retarded development(?)
Vaccinations	Fetal vaccinia
Phenothiazines	Hyperbilirubinemia(?); depression; hypothermia(?)
Antihistamines	Infertility(?)
Oral progestogens, androgens, and estrogens	Advanced bone age
Insulin (shock)	Fetal loss
Anti-thyroid drugs	Hypothyroidism
Polio vaccine, live	Fetal loss(?)

Source: Adapted from Schardein 1976, Drugs as Teratogens. CRC Press, Boca Raton, Florida. P 7 (Copyright The Chemical Rubber Co., CRC Press, Inc.)

adverse drug reactions make it likely that conspicuous effects will eventually be detected. Nevertheless, most of the effects listed in Tables IV-2 to IV-4 were initially reported only through case reports, and only a few appear to have been confirmed by rigorous epidemiologic methods. For example, the associations of thalidomide with phocomelia (Lenz and Knapp 1962, McBride 1961) and diethylstilbestrol with vaginal adenosis and adenocarcinoma (Herbst et al. 1971) were initially observed in case reports and later confirmed in epidemiologic studies. In addition, the reported effects appear to be biased towards malfunctions or malformations easily observed in neonates. Possible side effects of drugs on reproduction other than teratogenicity appear to have been subjected to comparatively little study.

2. Cigarette smoking. Maternal cigarette smoking is associated with a wide range of adverse effects on the mother, the fetus, and the newborn infant, including low birth weight, shortened gestation, spontaneous abortions, smaller placental weights in relation to birth weight, complications of pregnancy, increased perinatal mortality, lower age at menopause, and probably retarded physical growth and mental development up to the age of 11 years (USDHEW 1979a, Population Information Program 1979; see Appendix A). These conclusions are based on more than 50 studies involving a total of more than half a million births. Most of these associations are a result of smoking during pregnancy, and some are a result of smoking before pregnancy.

The most conclusive association is between cigarette smoking during pregnancy and low birth weight. Infants born to women who smoked 20 cigarettes per day during pregnancy are on the average 100 g lighter than infants born to nonsmokers (USDHEW 1979b, Kline et al. 1980a); infants of women who smoked 20-30 cigarettes per day before pregnancy but abstained during pregnancy are on the average approximately 30 g lighter (Rees et al. 1972). Reductions in birth weight were smaller in the offspring of women who smoked fewer than 20 cigarettes per day. Perinatal mortality showed similarly increased risks with smoking after the 4th month of pregnancy, but this association may not be independent of the association with low birth weight.

The effects of paternal smoking on reproduction have been examined in a few studies, one of which suggested that smoking leads to a decreased sperm count (Viczian 1969). Paternal smoking does not appear to be associated with decreased birth weight (Comstock and Lundin 1967).

3. Alcohol. Heavy consumption of alcohol by pregnant women is associated with a syndrome known as fetal alcohol syndrome, characterized by a cluster of facial abnormalities, growth retardation, central nervous system dysfunction, and such other malformations as skeletal, urogenital, and cardiac defects (Fabro 1978, U.S. Treasury/USDHHS 1980) and possibly with an increased risk of major malformations (Ouellette et al. 1977), although there is conflicting evidence (Kaminski et

al. 1976). Fetal alcohol syndrome has been estimated to occur in about 1 per 750 live births in the United States population (Streissguth et al. 1980), and several hundred cases have been recorded among the offspring of alcoholic women (U.S. Treasury/ USDHHS 1980, Hanson et al. 1978).

Decreased birth weight has been observed among children of women whose average alcohol consumption was two drinks per day (Russell 1976, Little 1977, Kaminski et al. 1976); this association appears to be independent of smoking (Kaminski et al. 1976). When this amount was ingested early in pregnancy, the decrease in birth weight was approximately 90 g, and when this amount was ingested late in pregnancy, the decrease was approximately 160 g.

Two studies provide evidence of an association between moderate alcohol consumption and spontaneous abortions; in one study the association was evident when women reported drinking twice a week or more (Kline et al. 1980b), and in the other study consumption of 1-2 drinks per day was associated with spontaneous abortion, particularly during the second trimester of pregnancy (Harlap and Shiono 1980). Paternal alcohol drinking has not been examined for possible effects on pregnancy outcome. Chronic alcoholism has been associated with testicular atrophy and other abnormalities (Hueper 1942, Turner et al. 1977).

4. Illicit and addictive drugs. The use of heroin and other addictive drugs by pregnant women can lead to withdrawal symptoms in their newborn infants. In one New York hospital,

it was estimated that 1 of every 27 babies delivered during 1972 showed signs of narcotic addiction (Rothstein and Gould 1974). Heroin, methadone, LSD, and other illicit or addictive drugs have been reported at various times to be teratogenic or to have other adverse effects on reproduction (Schardein 1976), but such potentially confounding factors as smoking and alcohol consumption have not been adequately controlled for. Heroin appears to be associated with fetal growth retardation, fetal infection, and perinatal mortality (Naeye et al. 1973, Clamon and Strang 1962). Maternal use of LSD, at least in impure form, appears to be associated with increased rates of spontaneous abortions and perhaps congenital malformations (Jacobsen and Berlin 1972, McGlothlin and Arnold 1971). Paternal use of marijuana and hashish appears to alter gonadal hormone levels and decrease sperm counts.

Investigation of such effects is complicated by the impossibility of documenting exposure, impurities and adulterants in the drugs as sold on the street, and poor nutrition and other health problems in users. The reports of teratogenic effects of these drugs were regarded by Wilson (1977) as more than ordinarily difficult to evaluate because of "abuse or misuse situations with attendant uncontrolled variables."

5. Exposures in the workplace. Tables IV-5 and IV-6 list a number of chemicals and groups of chemicals that have been reported to be associated with adverse reproductive effects in men and women exposed in the workplace. For nine selected

TABLE IV-5

CHEMICAL EXPOSURES REPORTEDLY ASSOCIATED WITH ADVERSE REPRODUCTIVE EFFECTS IN OCCUPATIONALLY EXPOSED MEN

Chemical	Reported Effects*	Comments
1,2-Dibromo-3-chloropropane (DBCP)	Infertility; azoospermia, oligospermia	See Appendix A
Lead and/or other smelter exposures)	Infertility, spontaneous abortions; premature births; Wilm's tumor; morphological and behavioral abnormalities in children; chromosomal abnormalities; sperm abnormalities	See Appendix A
Vinyl chloride	Chromosomal abnormalities	See Appendix A
Anesthetic gases	Increased spontaneous abortions and congenital abnormalities; ? change in sex ratio	See Appendix A
Kepone	Loss of libido; reduced sperm counts	NIOSH 1976
Boric acid	? Loss of libido; ? reduced sperm counts and elevated fructose in semen	Tarasenko et al. 1972
Carbon disulfide	Decreased libido; impotence; increased sperm abnormalities	Lancranjan 1972; see Appendix A
Ethylene dibromide	Decreased fertility	See Appendix A

*Including effects reported in wives and offspring of occupationally exposed men

Source: Summarized from Sullivan and Barlow 1979

TABLE IV-6

CHEMICAL EXPOSURES REPORTEDLY ASSOCIATED WITH ADVERSE REPRODUCTIVE EFFECT IN OCCUPATIONALLY EXPOSED WOMEN

Chemical	Reported Effects	Comments
Lead and/or other smelter exposures)	Menstrual disorders; increased spontaneous abortions; reduced birth weights; ? congenital abnormalities	See Appendix A
Mercury (metal)	? Abnormal ovarian function	Panova and Ivanova 1976
Selenium	? Spontaneous abortions; ? congenital malformation	Robertson 1970
Cadmium	? Reduced birth weight	Tavetkova 1970
Beryllium	? Pregnant women at high risk of acute poisoning	Hardy 1965
Anesthetic gases	Spontaneous abortions; reduced birth weights congenital malformations; ? infertility	See Appendix A
Carbon monoxide	Fetal death or brain damage	Longo 1970
Phthalate esters	? Anovulation; ? increased spontaneous abortions	Aldyreva et al. 1975
Formaldehyde	Menstrual disorders; toxemia and anemia in pregnancy; increased spontaneous abortions; reduced birth weights	Shumlina 1975
Carbon disulfide	Menstrual disorders; increased spontaneous abortions; ? reduced fertility	Wiley et al. 1936, Ehrhardt 1967; see Appendix A

TABLE IV-6 (continued)

Chemical	Reported Effects	Comments
? Caprolactam	Menstrual disorders; impaired childbearing	Martynova et al. 1972
Organochlorine pesticides	Abnormal ovarian function; increased toxemia of pregnancy; impaired lactation	Blekherman and Ilyina 1973; Veis 1970; Mukhametoya and Vozovaya 1972
? Styrene	Menstrual disorders, increased toxemia of pregnancy	Zlobina et al. 1975
Benzene, toluene, xylene	Prolonged menstrual bleeding	NIOSH 1973
Laboratory solvents	Chromosome aberrations; ? birth defects	See Appendix A
Pesticides (various)	Impotence; chromosome aberrations	See Appendix A

Source: Summarized from Sullivan and Barlow 1979

chemicals posing workplace hazards, the scientific evidence for reproductive impairment is summarized in Appendix A.

The studies that support the conclusions in Tables IV-5 and IV-6 vary widely in nature and extent. A series of Russian studies were primarily cohort studies of women working with the chemicals (see Appendix A); a range of outcomes was examined, including endocrine functions, menstrual patterns, and pregnancy outcomes. These studies are difficult to evaluate, because the published data often provide insufficient detail describing the cohort studied and the methods of data collection.

The majority of studies of pregnancy outcomes that were conducted in the United States and Europe were case-control studies. Several of the cited studies involved small groups of highly exposed workers (e.g., those for kepone, boric acid, and carbon disulfide) or clusters of case reports (e.g., those for beryllium and carbon monoxide). Only six of the groups of chemicals reviewed in Appendix A have been examined in a number of studies.

Anesthetic gases. Of 14 studies of anesthetics, maternal exposure was associated with spontaneous abortions in 9 of them (Askrog and Harvald 1970; Vaisman 1967; Rosenberg and Kinves 1973; Cohen et al. 1971, 1980; Cohen 1974; Knill-Jones et al. 1972, 1975; American Society of Anesthesiology 1974); and one study did not detect an association (Pharoah et al. 1977). Maternal exposure also was associated with low birth weight (Askrog and Harvald 1970, Rosenberg and Kinves 1973, Pharoah

et al. 1977), but the evidence for an association with stillbirths (Knill-Jones et al. 1972, 1975, Pharoah et al. 1977) and congenital malformations (Askrog and Harvald 1970, Corbett et al. 1974, Knill-Jones et al. 1972, American Society of Anesthesiology 1974, Pharoah et al. 1977, Cohen et al. 1980) is less consistent. The definitions of exposure have varied among studies, however, and it is not possible to determine whether these effects, if any, are due to exposure before or during pregnancy.

The evidence for effects of paternal exposure to anesthetics is less consistent. In two studies, paternal exposure was associated with spontaneous abortions (Cohen 1974, Cohen et al. 1975), but two of three other studies failed to detect an association (Knill-Jones et al. 1975, American Society of Anesthesiology 1974) and one showed a questionable association (Askrog and Harvald 1970). These findings raise the possibility that nitrous oxide, rather than halothane, is associated with spontaneous abortions, since exposure in the positive studies was to nitrous oxide, whereas exposures were varied in the other studies. Evidence for an association between paternal exposure and malformations is inconsistent, with some positive and some negative findings (American Society of Anesthesiology 1974, Knill-Jones et al. 1975, Astrog and Harvald 1970). Effects other than spontaneous abortions are listed in Tables IV-5 and IV-6 if they were significant in one or more studies, even though they were not consistently observed. The most important anesthetic gases are halothane and nitrous oxide, and NIOSH

estimates that over 200,000 workers are exposed to various anesthetic gases (NIOSH 1977c).

Lead and other smelter emissions. The increased risk of spontaneous abortion and stillbirth resulting from maternal exposure to lead has been recognized for nearly a century (Oliver 1911, Holt 1923, Lane 1949). Five studies have indicated a wide range of adverse effects in occupationally exposed women and in their offspring (see Appendix A). Intrauterine growth retardation, postnatal convulsions, mental retardation, macrocephaly, encephalopathy, hyperactivity, and anemia are all probably associated with chronic maternal lead exposure (Moore et al. 1977, Beattie et al. 1975, Hunt 1979). Three studies suggest that pregnancy outcome may be affected as a result of paternal exposures or exposures to both parents (Nordstrom et al. 1979a,b; Nogaki 1958). Wilm's tumor in offpsring has been shown to be associated with paternal exposure in the workplace (Kantor et al. 1979). Sperm count, morphology, and mobility are probably impaired by occupational exposure to lead (Lancranjan et al. 1975). Chromosomal abnormalities appear to be associated with occupational exposures (Nordenson et al. 1978b, Schwanitz et al. 1970), although one study failed to detect an association (O'Riordan and Evans 1974). However, the impact of these chromosomal effects on pregnancy outcome is not known.

In many studies, male and female workers were also exposed to arsenic, cadmium, or other smelter fumes. It is possible that the observed effects, therefore, should be attributed

in part or in whole to these chemicals and their interactions (Lauwerys et al. 1978, Nordenson et al. 1978a).

Vinyl chloride. An association between exposure of men to vinyl chloride in the workplace and fetal loss in their wives has been suggested (Infante et al. 1976b, Waxweiler et al. 1977). However, when account is taken of reproductive problems before their husbands' exposure, the excess risk reported by Infante et al. (1976b) is no longer significant (Kline and Hatch 1980). Seven studies of exposed workers (presumably all males) have shown increases in the frequency of chromosome aberrations (Purchase et al. 1978, Heath et al. 1977, Funes-Cravioto 1975, Hansteen et al. 1978, Szentesi et al. 1976, Ducatman et al. 1975, Fleig and Thiess 1978), although one large, well-controlled study failed to detect an association (Picciano et al. 1977). The significance of these findings for pregnancy outcome is uncertain, however, and the question of fetal loss or other reproductive effects resulting from paternal exposure to vinyl chloride in the workplace remains open (see a discussion of environmental exposures below).

1,2-Dibromo-3-chloropropane (DBCP). Six studies of exposed men have shown consistent reductions in sperm count, sometimes accompanied by adverse effects on fertility (Whorton et al. 1977, 1979, Sandifer et al. 1979, Kapp et al. 1979, Glass et al. 1979, Potashnik et al. 1978). One study in Israel reported increased fetal loss in wives of DBCP applicators (Kharrazi et al. 1980).

Other effects on reproduction, including possible effects from maternal exposure, apparently have not been investigated.

Laboratory chemicals and pesticides. Two studies have indicated that the children of female workers exposed to laboratory chemicals and solvents may suffer an increased incidence of congenital malformations (Meirik et al. 1979, Holmberg 1979). Similarly, female chemical workers may be subject to an increased risk of spontaneous abortions (Hemminki et al. 1980). Chromosome aberrations have been reported in the children of women laboratory workers (Funes-Cravioto et al. 1977). The specific chemicals responsible for these effects have not been identified.

Impotence, chromosome aberrations, infertility, miscarriage, and several other adverse effects on reproduction have been reported in men and women occupationally exposed to various pesticides (Espir et al. 1970, Yoder et al. 1973, Shabati et al. 1978, Kiraly et al. 1979, Nikitina 1974). In none of these studies could the amount, duration, or type of pesticide exposure be clearly identified (see Appendix A).

Conclusions. The studies cited in this section on workplace hazards indicate that a number of chemicals adversely affect the reproduction of male and female workers exposed to them. A wide range in types of effect has been recorded (Tables IV-5 and IV-6). However, it is difficult to generalize about the significance of occupational exposures, for two reasons. First, ideal epidemiologic studies of exposed workers are difficult to conduct. Second, comparatively few thorough studies have

been conducted, and these have varied considerably in methodology. When extensive studies have been conducted (e.g., those for lead or anesthetic gases), a number of different types of effects have been identified. However, in other cases (e.g., DBCP) only one type of effect was investigated. Thus, although the data cited here suggest that workers in certain occupations are exposed to substantial risks, the full magnitude of the problem is difficult to define without further study and evaluation.

6. Environmental chemicals and food contaminants. There is some evidence suggesting adverse reproductive effects of several environmental chemicals and contaminants. The reports fall into three classes according to the mode of exposure:

a. Neighborhood pollution. A series of studies suggested an increased rate of spontaneous abortions and a reduction in birth weights among the population residing close to a metal smelter in Sweden (Nordstrom et al. 1978a,b, 1979a,b). The major products of the smelter were arsenic, copper, lead, sulfuric acid, and sulfur dioxide. Another study suggested that low-level maternal exposure to lead is associated with prematurity (Fahim et al. 1976). The results of a study by Infante et al. (1976) suggested that proximity to a vinyl chloride plant might be associated with a range of central nervous system and other malformations. However, two case-control studies indicated that the neural tube defects in offspring, which were high in the area, were not related to occupational exposures of parents (Edmonds et al. 1975, 1978).

b. Accidental food contamination. Studies have been made of several incidents in which local food supplies were highly contaminated with toxic chemicals. Exposure to methylmercury in two independent incidents (Japan and Iraq) led to the birth of infants with morphological and central nervous system abnormalities (NRC 1978, Bakir et al. 1973, Amin-Zaki et al. 1976). Following maternal exposure to hexachlorobenzene in an incident in Turkey, children developed skin lesions and 95% died within a year of birth (Peters 1976); many stillbirths were also reported (Courtney 1979). In both these cases, infants exposed in utero and via maternal milk were affected more severely than adults. In contrast, infants prenatally exposed to polychlorinated biphenyls and polychlorinated dibenzofurans in an incident in Japan were affected less severely than adults, although the long-term prognosis for these children is still unknown (Kuratsune et al. 1972, 1976). (In a fourth incident of this type, the contamination of food in Michigan with polybrominated biphenyls, we know of no definitive report of adverse reproductive effects.)

c. General environmental pollutants. Studies of possible effects of general environmental pollutants on human reproduction appear to be scanty. There is one report of an association between premature births and exposure to DDE (1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene) (O'Leary et al. 1972). However, this association was based on the concentration of DDE in maternal blood and does not necessarily imply a cause-and-effect relationship;

furthermore, no relationship was found between spontaneous abortions and DDE levels (O'Leary et al. 1970).

Conclusions

At least 40 drugs and at least 20 other chemicals have been associated with reproductive impairment in humans under various conditions of exposure (Tables IV-2 to IV-6). Reported effects range from disturbance of endocrine function or loss of libido to spontaneous abortions, birth defects, perinatal death, or retarded development. Exposure to a number of known agents (lead, mercury, PCBs, cigarettes, and alcohol) and some suspect agents (marijuana, DDE) is common and widespread. Some occupational exposures have been reported to involve substantial risks to the workers involved. However, it is very difficult to estimate the overall significance of all types of chemical exposures, because of the limited nature of the available studies. Only a few chemicals have been studied, rarely by rigorous epidemiologic methods, and only a few potential effects have been investigated in these studies. These factors should be borne in mind when assessing the potential importance of chemicals in contributing to reproductive impairments and losses.

V. EXPERIMENTAL ASSAYS FOR THE EFFECTS OF CHEMICALS ON REPRODUCTION

There are a number of experimental assay systems for investigating the potential effects of chemicals on reproduction in mammals. Some of these assays have been developed primarily to investigate biological and biochemical mechanisms of action, whereas others have been developed primarily as test systems for routine screening of chemicals for potential hazards to human reproduction. This chapter is principally concerned with the latter type of test system. Chapter VI will discuss the extent to which these screening systems have proved to be useful in identifying potential hazards and in predicting actual effects in humans.

The experimental assay systems discussed in this chapter have been standardized to various degrees. The first section summarizes assays that can be conducted in humans; these tests have not been standardized and are not used on a routine basis. In the second section, there is a summary of three widely used routine assays; there is general scientific agreement on the protocols that should be followed in conducting these tests. The third section of the chapter describes a number of in vivo tests that have not been standardized to the point where they are now used routinely, although they have been used to investigate the effects of a number of chemicals. The fourth section describes a number of in vitro tests. Some of the latter tests

appear to be highly relevant to the measurement of reproductive effects in vivo; others are still in the research stage.

Table V-1 lists 16 tests that have been used to investigate reproductive effects in vivo. The table specifies the end points measured in each test and provides brief comments on dosing, species, and other relevant factors. Tables V-2, V-3, and V-4 list in vitro tests and the end points measured in each, with pertinent comments on other aspects of the tests.

Assays in Humans

Several of the assays listed in Tables V-1 and V-2 measure end points that may be relevant to human reproductive functions. Although they have not often been used to investigate possible adverse effects of chemicals, they can be used in appropriate circumstances, e.g., when humans have been treated with drugs or have been exposed to environmental or occupational chemicals.

End points in humans for reproductive toxicity tests that are reasonably objective and do not cause significant discomfort include blood and urine hormone levels. Radioimmunoassays exist for the human pituitary gonadotropins FSH and LH (Millar and Aehnelt 1977, Monroe et al. 1968) and for androgens (Kimouchi et al. 1973) and estrogens (Korenman et al. 1969). In neonates or prepubertal children, measurement of plasma growth hormones may be useful in assessing retardation of bone growth or stunting. Gynecologic-obstetric medical histories provide information about ovulation, menstruation, and fecundity, but this type of information is often sought only after women have been exposed

TABLE V-1. AVAILABLE IN VIVO TEST SYSTEMS FOR MEASURING REPRODUCTIVE TOXICITY

Test	Species	Dosing	End points	Comments	References
Teratogenicity	Rat, mouse, rabbit; sometimes others	Usually by gavage to pregnant females, during period of fetal organogenesis; two or more dose levels,one approaching maternal toxic level	Resorptions, fetal toxicity, fetal growth, morphologic and functional abnormalities, etc.	Critical period for exposure dependent on species; functional, behavioral, or biochemical effects on offspring investigated by some studies	NAS 1975, 1977; USEPA 1978; USFDA 1966, 1970; WHO 1967; OECD 1979
Three generation test	Usually rodents	Continuous, usually in feed, through three generations; two or more dose levels, one giving minimal maternal toxic effects	Male and female fertility, maternal toxicity, fetal survival, fecundity, neonatal survival, neonatal growth and maturation, organ weights and pathology, multigeneration effects, mutagenic effects	Tests for effects manifested through second and third generation--i.e., in animals exposed in utero and via lactation; behavioral and biochemical effects sometimes observed; can reveal transplacental carcinogenesis; some protocols provide opportunity to differentiate maternal and paternal effects	NAS 1975, 1977; USEPA 1978; USFDA 1966, 1970; WHO 1967; OECD 1979
Dominant-lethal assay	Rodents	Untreated females inseminated by male previously treated with toxic agent at near-toxic doses	Pregnant females sacrificed and the number of live, dead, and resorbed fetuses counted	Mutagenic effect evidenced by presence of dead or resorbed fetuses (see also Table V-4	Bateman 1977

TABLE V-1 (continued)

Test	Species	Dosing	End points	Comments	References
Sperm counts*	Mammals (males)	Multiple treatments of male	Number of sperm/unit volume and volume of ejaculate	Readily collected and counted; male cycle may lead to fluctuation	Amelar et al. 1977
Sperm motility (also morphology)*	Mammals (males)	Multiple treatments of male	Viability of sperm	View with microscope	Amelar et al. 1977
Semen chemistry*	Mammals (males)	Multiple treatments of male	Fructose, electrolytes, enzymes, etc.	Must take into account variations in chemical composition among species	Amelar et al. 1977
Spermatogenesis*	Mammals (males)	Multiple treatments of male	Presence of sterile seminiferous tubules of testes	Histologic evaluation, biopsy	Amelar et al. 1977
YFF test*	Mammals (males)	Variable treatments of male	Presence of more than one fluorescent spot in sperm cells after addition of fluorescent marker, which indicates an additional Y chromosome as a result of chromosome nondisjunction	Nondisjunction increased by mutagens	Hegde et al. 1978, Kapp and Jacobson 1980

TABLE V-1 (continued)

Test	Species	Dosing	End points	Comments	References
Cytogenetic analysis of germ cells	Mammals	Variable treatments of male or female	Chromosome aberrations in spermatogonia, spermatocytes, or oocytes	Chromosome damage likely to have adverse effect on reproduction	Brewen et al. 1978
Heritable translocation test	Rodents (males)	Variable treatments of male	Reduced fertility with cause (reciprocal chromosome translocation) confirmed by cytogenetic analysis of germ cells	Reciprocal translocations are possible but probably not major cause of reduced fertility	Generoso et al. 1978
Amniocentesis*	Humans	Environmental exposure	Level of α-fetoprotein in amniotic fluid and chromosome analysis of fetal cells	Can detect various congenital defects including spina bifida, anencephaly, Down's syndrome and other chromosome anomalies	Hogarth 1978, Schlesselman 1979
Androgen blood levels*	Mammals (usually male)	Usually multiple treatments	Abnormal blood levels of androgens	Measure of male sex steroids	Kimouchi et al. 1973
Estrogen blood levels*	Mammals (usually female)	Usually multiple treatments	Abnormal blood levels of estrogens	Measure of female sex steroids	Korenman et al. 1969

TABLE V-1 (continued)

Test	Species	Dosing	End points	Comments	References
FSH (blood)*	Mammals	Usually multiple treatments	Abnormal blood levels of follicle stimulating hormone	Radioimmunoassay	Millar and Aehnelt 1977, Monroe et al. 1968
LH (blood)*	Mammals	Usually multiple treatments	Abnormal blood levels of luteinizing hormone	Radioimmunoassay	Millar and Aehnelt 1977, Monroe et al. 1968
Uterine weight	Mammals (females)	Usually multiple treatments	Stimulation of weights indicative of estrogenicity	Ovariectomized animals used	Zarrow et al. 1964
Seminal vesicle weights	Mammals (males)	Usually multiple treatments	Stimulation of weights indicative of androgenicity	Castrated animals used	Zarrow et al. 1964

* May be performed with humans

TABLE V-2

IN VITRO TESTS FOR TOXICITY TO MAMMALIAN SPERM AND OVA

Test	End Point Measured	Relevance to Humans	Comments	References
Sperm motility assays (animal or human ejaculates)	Direction and speed of sperm progression in microscopic field	Even if human sperm used, may not provide direct evidence of human risk; uncertainty because bioavailability of chemical unknown	Treatment of semen with chemicals may provide an inexpensive, rapid, and objective screen	Amelar et al. 1977.
Rate of in vitro penetration of eggs by sperm treated with the test compound in a system to support capacitation or pretreated before capacitation (mouse, rat)	Proportion of eggs penetrated by sperm and effect on subsequent stages	Potentially useful indicator of damage to sperm by chemicals affecting capacitation and later stages; could detect damage induced before or during capacitation	Inexpensive, rapid, objective test; can detect effects of in vivo exposure in males	Fraser 1979
Insemination of female with sperm treated in vitro (combination of technique described in preceding entry with artificial insemination)	Success of the "mating" (either (embryos or offspring)	Relevance limited because of unnatural fertilization; uncertainty because bioavailability of chemical unknown	Inexpensive, straightforward test	Tsunoda and Chang 1976

TABLE V-2 (continued)

Test	End Points	Relevance to Humans	Comments	References
Fully in vitro fertilization assays (sperm capacitation and in vitro fertilization; mouse, rabbit, rat)	Proportion and extent of fertilization of ova (e.g., early cleavage stages) in vitro, or embryonic development if implanted after treatment	Has been used for assessing toxicity to mammalian male reproductive tract; could assess damage to gametes of both sexes before fertilization	Methodology well established; rapid, inexpensive; may be adaptable as a screen for chemicals	Brackett 1978
Human leukocyte migration tests (leukocytes from human females with human sperm in vitro)	Inhibition of sperm migration, immune response of female to the male, or toxic or inhibitory factors in the male	Used in testing infertile couples; suitable for use as a screen for agents causing male or female immune-related infertility	Rapid, inexpensive; proven successful in infertility studies, but usefulness restricted to agents acting through immune system; has not yet been used as assay for chemicals	Soffer et al. 1976
Heterologous in vitro fertilization test (e.g., human sperm with hamster egg)	Penetration of animal ova in vitro	Superior to classically determined sperm parameters in predicting subfertility in human male	Rapid, inexpensive; should be adaptable for use as a screen for chemicals	Hall and Dixon 1980

TABLE V-3

IN VITRO TESTS FOR TERATOGENICITY

Test	End Points	Relevance to Humans	Comments	References
Postimplantation culture of embryo in vitro (e.g., in vivo fertilization in rat, followed by explantation and culture of 10-day conceptuses)	Developmental defects in embryo	Specifically assesses induction of morphological or biochemical defects in mammalian embryonic development	Can distinguish direct effects from maternally or placentally mediated effects; allows early development through organogenesis, which is similar to in vivo growth; techniques broadly disseminated and standardized; recently simplified, but still requires appreciable skill and time; responses less variable than in vivo treatment; gestational events later than organogenesis not monitored	New 1976, Neubert and Barrach 1977, Sanyal et al. 1980
Preimplantation culture of mammalian embryo in vivo (e.g., in vitro fertilization and embryonic growth to a stage suitable for implantation and in utero growth to term, or simple inspection without implantation)	Developmental defects induced or expressed in early embryonic stages	Same as for preceding entry	Similar to preceding entry, but allows inspection of very early events; relatively unperfected compared to postimplantation techniques	Mukherjee 1974

TABLE V-3 (continued)

Test	End Points	Relevance to Humans	Comments	References
In vitro organ culture (mammalian or avian; best results with small nonvascularized organs)	Defects in development of organ appearing postexcision	Specifically assesses induction of morphologic defects in organogenesis in mammals, including humans (see next entry)	Successfully used to measure drug effects; limited by failure of cultured organs to follow closely in vivo growth patterns and by difficulty making objective measurements or meaningful interpretations of induced effects; relatively difficult techniques	Wilson 1978
In vitro tissue culture with material from aborted human embryos	Defects in organ development	Human tissue used in test	Directly assesses effects in human tissue; technical difficulties compounded by moral and ethical issues	Shepard and Pious 1978

TABLE V-3 (continued)

Test System	End Points	Relevance to Humans	Comments	References
In vitro culture of human tissue (e.g., male prepuce, biopsy material, kidney fibroblasts obtained postmortem, other fibroblasts)	Inhibition of cell growth; direct cellular toxicity	Possibly a close relationship between degree of inhibition of cell growth and teratogenicity of a compound (as has been demonstrated for some cancer chemotherapeutic drugs)	Potentially a quick, inexpensive, objective screen; needs further validation to establish relationship between growth inhibition and reproductive toxicity	Shepard and Pious 1978
Culture of lens epithelial cells from day-old chicks in amniotic fluid from treated pregnant mice	Profiles of crystalline (structural proteins) synthesis measured by autoradiography in electrophoretic gels	May provide a general screen; end point more biologically specific than is end point for preceding entry	Tests substances metabolized by pregnant mice; validated for two teratogenic agents; may be limited by metabolic pathways in other tissues differing from those in the tissue in this assay	Clayton 1976

TABLE V-4

IN VITRO AND OTHER SHORT-TERM TESTS FOR GENOTOXICITY AND EMBRYOLETHALITY

Test	End Points	Relevance to Humans	Comments	References
Dominant lethal tests; in vivo exposure of male gametes (see also Table V-1)	In mice, reduced litter size, dead or resorbed fetuses; in Drosophila, proportion of unhatched eggs ("white") or dead embyros ("brown")	Ostensibly tests for lethal male mutations; nongenetic effects lethal to the embryo or fetus also measured by the same end points; chromosome aberrations and other dominant lethal genetic effects possibly important etiological factors in human fetal wastage as well as in birth defects	Classical techniques with standard protocols; inexpensive, reliable, easily interpreted systems with Drosophila; mouse system less so; difficult to distinguish genetic dominant lethality from embryotoxic events, but may not be a drawback for screening	Bateman 1977
Cytogenetic analysis of germ cells	Chromosome aberrations in spermatogonia	Chromosome aberrations in a high proportion of human abortuses	Established test system, particularly in males	Brewen et al. 1978
Heritable translocation test	Reduced fertility with reciprocal chromosome translocation confirmed by cytogenetic analysis of sperm	Reduced fertility in humans and other mammals likely to be caused in part by reciprocal translocation	Mechanism of reduced fertility understood, but probably not major cause of reduced fertility in humans	Generoso et al. 1978

Test System	End Points	Relevance to Humans	Comments	References
Germ cell DNA repair assays (in vivo treatment of male mice, followed by excision of spermatogenic tissue at different stages)	DNA damage, as measured by alkaline elution analysis (molecular size), or unscheduled DNA synthesis	Damage and subsequent repair of DNA in male germ cells is an index of potential interference with reproduction	Quick, objective; more research needed; not completely validated as predictor of toxicity to embryo	Lee et al. 1980
Combinations of in vivo and in vitro techniques (e.g., in vivo mutagenesis and mating followed by in vitro culturing of resultant embryos); see table on in vitro tests for teratogenicity	Embryonic (somatic) expression of mutant genes including dominant and recessive lethals and visible traits that influence organogenesis	Could be used to determine which kinds of environmental mutagens would be particularly hazardous to embryo and at which stages (e.g., could distinguish agents likely to induce lethality from those with potential for teratogenicity)	Requires the difficult techniques of embryo culture and in vivo testing, but increases flexibility in measurable end points	Pederson and Goldstein 1979
Host-mediated assay for malignant cell transformation as a result of transplacental exposure (pregnant hamsters treated and primary cultures made of minced fetuses)	Morphologic transformation of the cultured fetal cells (atypical colonies on plastic surface or growth in soft agar)	Inferentially relevant to human transplacental carcinogenesis	Rapid, relatively inexpensive; may be limited as a screen by marked species differences in transplacental susceptibilities to different carcinogens	Rice 1976

to an agent suspected of causing endocrine imbalances or other problems.

In males, sperm counts, motility, and morphology can be used as end points, but generally their usefulness is restricted to instances when the chemical is overtly toxic to germ cells. These end points, therefore, are of little value when the agent's actions are more subtle. Testicular biopsies can aid in establishing why a man is sterile, but such procedures cannot be performed routinely. Examination of the composition of ejaculated sperm or of uterine fluid or milk can provide some additional biochemical information about exposure to chemicals and may be useful in drawing conclusions about the actions of toxic chemicals upon reproductive processes. Amniocentesis has been used to determine such severe fetal defects as spina bifida (indicated by the presence of α-fetoproteins), and ultrasound can be used to determine intrauterine fetal growth retardation or placental insufficiency.

Teratogenicity Tests in Mammals

Tests for teratogenicity have been standardized to a greater degree than any other test of reproductive impairment. Protocols for the appropriate conduct of these tests have been published by several expert groups (NAS 1975, 1977; Health and Welfare Canada 1975; USFDA 1970; USEPA 1978; OECD 1979; WHO 1967). These guidelines, and those adopted by other national regulatory agencies, show close agreement in their detailed requirements for drug testing (see Table V-5).

Tests are usually conducted in rats, mice, hamsters, or rabbits; other small mammalian species and primates are sometimes used, although the use of primates is limited by their cost and availability. For safety testing, at least two species are recommended.

The Food and Drug Administration guidelines (USFDA 1970), which are more extensive than other common protocols because they investigate end points other than birth defects, specify three testing phases (Figure V-1). Phase I consists of treating male animals for 60 days and females for 14 days before mating. The treatment of the pregnant females continues throughout gestation and weaning. The parameters assessed include breeding, fertility, implantation, fetal death, parturition, lactation, and neonatal effects. In Phase II, inseminated females from two species are treated during organogenesis; fetuses are removed by cesarean section 1 day before term (to prevent maternal cannibalism) and examined for morphologic malformations. In Phase III, pregnant animals are being treated from the final third of gestation through weaning to elucidate any effects on late fetal development, labor, lactation, and viability and growth of the offspring. The FDA guidelines require that there be at least two dose levels at each phase and that at least two species be studied, with 20 rodents and 10 nonrodents in each treatment group. Other sets of guidelines require three

TABLE V-5

TERATOGENICITY TESTING REQUIREMENTS AND RECOMMENDATIONS

	U.S.A.	France	Canada	Sweden	England	W.H.O.	Germany
Type of study	Before mating to weaning Critical period Perinatal	During pregnancy, with some taken to weaning	2 of 3: before and during gestation Critical period during gestation	Critical period Perinatal	Critical period	Critical period, some taken to weaning	Before mating to weaning Critical period Perinatal
Number of species	2	3	2 (1 nonrodent)	2	2 (1 nonrodent)	?	3
Animals	Rat; mouse or rabbit	Rat, mouse, rabbit	Rabbit; mouse, rat, or hamster	Rat, rabbit	Rabbit; rodent[a]	Mouse, rat, rabbit most used[c]	Mouse, rat, rabbit
Number of dose levels	2	3	3[b]	2	3	At least 3	2 or 3
Number of animals per dose level	10 rabbits 20 rodents	Large enough for statistical analysis; 50 minimum	20 rodents 10 nonrodents	?	?	Sufficient to reproduce and analyze	20 mice or rats; 8 to 10 rabbits
Comments		Emphasis on embryolethality, teratogenicity	Emphasis on teratogenicity	Maternal toxicity important			

[a]Evidence of susceptibility to known teratogen required.
[b]Plus two contol groups.
[c]Primate use advocated.

Source: Adapted from Schardein 1976, Drugs as Teratogens. Boca Raton, Florida. P 11

FIGURE V-1

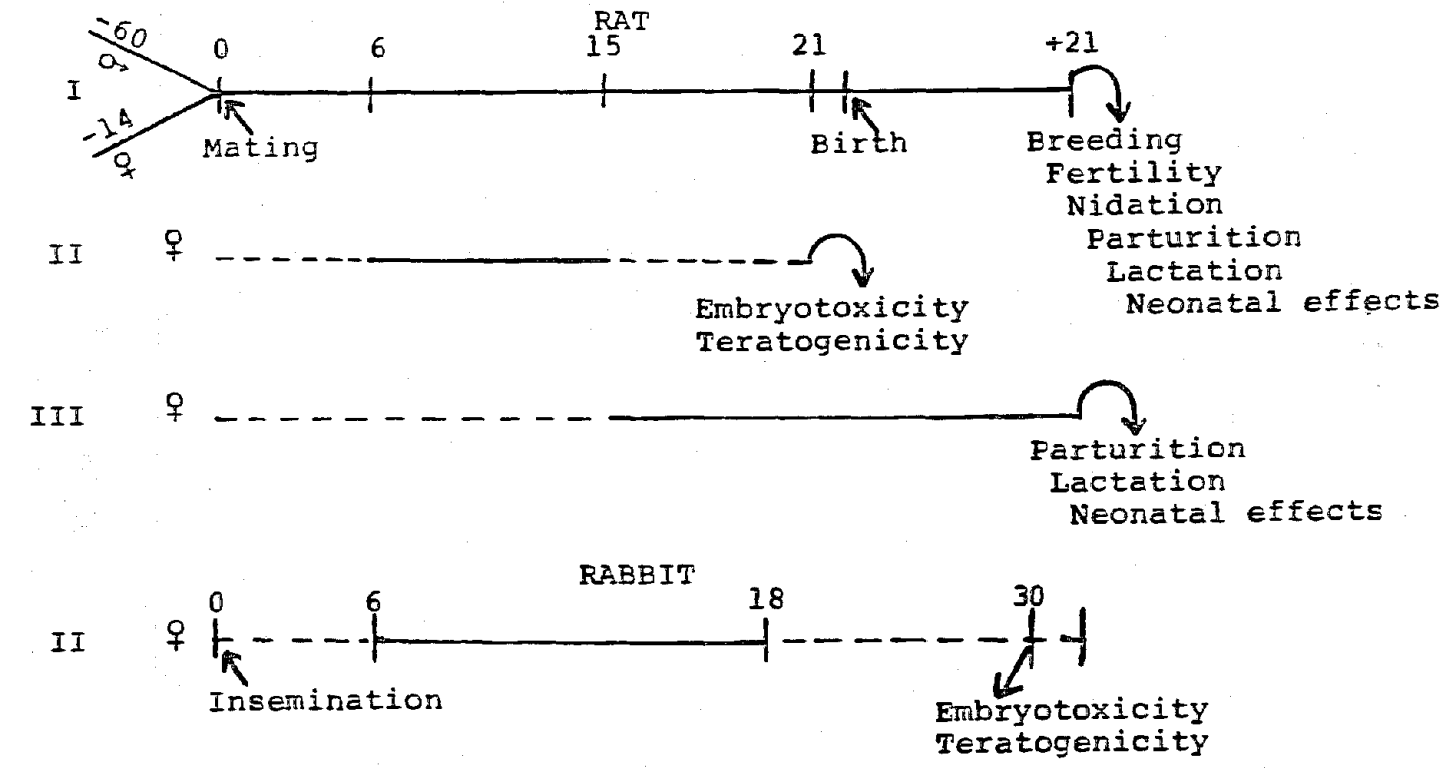
DIAGRAM OF A TYPICAL REPRODUCTION STUDY TO SCREEN

A DRUG FOR TERATOGENIC POTENTIAL

The tests are performed on the indicated study days.

Drug treatment is represented by the solid lines.

HASE



Source: Adapted from Schardein 1976, Drugs as Teratogens. CRC Press, Boca Raton, Florida. P 10 (Copyright The Chemical Rubber Co., CRC Press, Inc.)

or more dose levels. The highest dose level is selected to be just below the level that induces toxic effects in the mother. Lower doses are selected to include at least one that is expected to be a "nontoxic" dose in the fetus.

As of 1976, teratogenicity tests had been carried out for about 2,000 chemicals, primarily drugs, along with some pesticides and a few other chemicals. About one-third of these chemicals had shown teratogenic effects in experiments of various designs (Schardein 1976).

Until recently, teratologic studies focused almost exclusively on the development of gross structural abnormalities that were present at birth. However, the development of the central nervous system occurs over a protracted period of time, extending well into the postnatal period for both the human and animal brain. During these later stages of development, synaptic circuits are elaborated that are integral to complex functions. Teratogens may either kill neurons or disrupt the neurochemical development of these brain circuits, not producing gross morphological defects, but disrupting the normal functioning of the brain. During recent years, it has become increasingly apparent that exposure to a wide variety of chemicals, either during pregnancy or during early postnatal life, produces functional impairments, particularly behavioral deficits, in the absence of observable structural malformations. The study of these more subtle functional deficits is the domain of behavioral teratology (Spyker 1972a). Disruption of the normal

development of the nervous system has been associated with abnormalities in the behavior of offspring, including disturbances in arousal (i.e., depression, hyperactivity), learning disabilities, impaired motor function, and mental retardation (Hutchings 1978). Although there are certain to be neurochemical, if not structural, correlates of these behavioral alterations, behavioral analysis is likely to provide the most sensitive index of these alterations (Rodier 1978).

Behavioral indices of toxicity to the developing nervous system may therefore be the most sensitive screens for reproductive hazard to the brain. First, such agents as drugs that are nonteratogenic by traditional teratological screening procedures produce behavioral impairments in offspring (Coyle et al. 1976, Vorhees et al. 1979). Second, behavioral alterations are often detectable with doses of agents that are below those producing teratogenesis. In this case, behavioral deficits provide an early warning signal for such agents as methylmercury, which are teratogenic at higher doses (Spyker 1972a). The behavioral consequences of the fetal alcohol syndrome is another example of this sensitivity (Abel 1980).

Behavioral screening methods have already proven to be sensitive to a wide range of toxicants, such as drugs, alcohol, pesticides, and heavy metals. These results warrant the inclusion of postnatal behavioral evaluation in any assessment of chemical hazards to human reproduction. The FDA guidelines for tests that evaluate toxicant exposure from before mating

through lactation provide an exposure paradigm during which the central nervous system is vulnerable to insult, damage which may only be detected by evaluating behavioral function. Procedures for postnatal behavioral evaluation are now part of the guidelines for drug testing in Britain, France, and Japan.

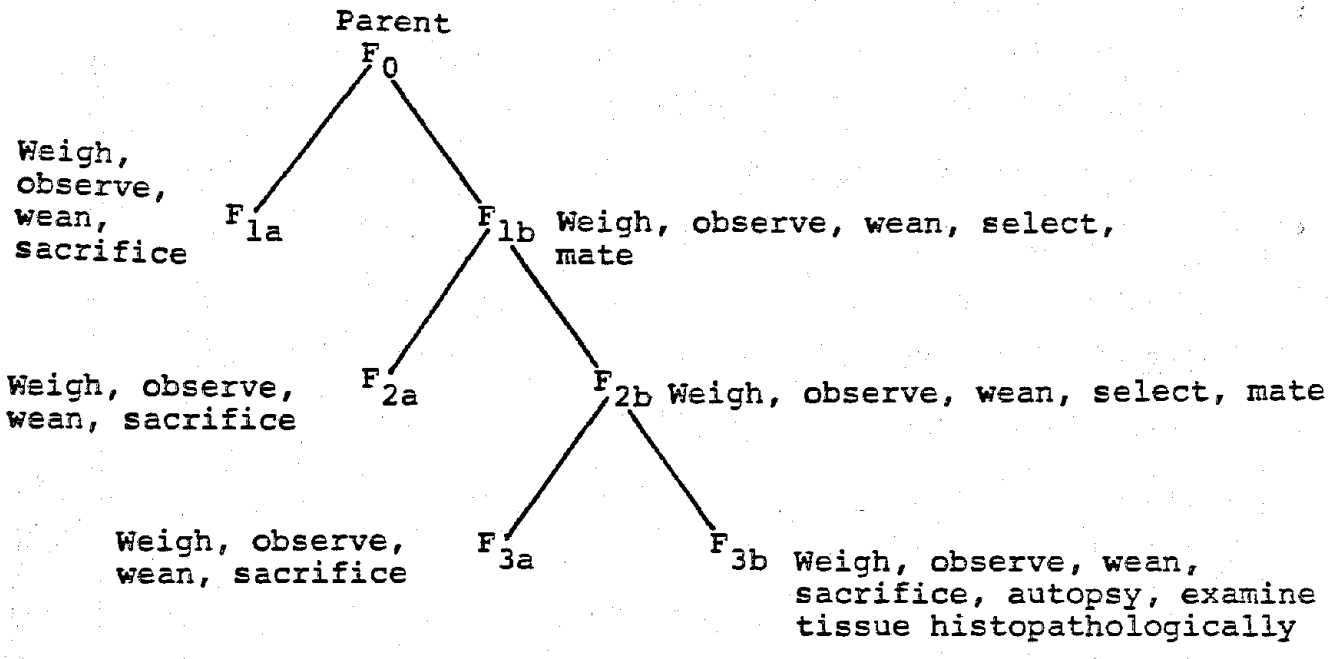
Three-Generation Reproduction Tests in Mammals

In this assay, groups of test animals, usually rats, are exposed to the test agent, usually in the diet, continuously through three generations. A typical plan for such a study is shown in Figure V-2. The purpose of conducting the study for more than one generation is to test for cumulative effects, e.g., effects attributable to exposure in utero and via lactation. Mutagenic effects may be detected in the second and third generation, although the system is now regarded as an insensitive screen for mutagenicity. In many tests, each generation is mated twice and studies of effects on the fetuses are limited to the second litters because of variability in reproductive performance in the first mating. Usually there are two or three dose levels, the highest selected to yield minimal toxic effects in the mothers and the lowest designed to be a no-effect or minimal-effect level in the fetus.

As additions to the basic design of the experiment, groups may be used in which untreated males are mated to treated females, and vice versa; this would help to establish whether a chemical acts only through one parent. Also, some of the pups may be

FIGURE V-2

PLAN FOR A THREEE-GENERATION REPRODUCTION STUDY



Source: Adapted from USFDA 1970

cross-fostered at birth to treated and untreated females to investigate the effect of the chemical transmitted in milk.

A wide variety of end points is measured in both parents and offspring in each generation (see Table V-1). Such experiments usually generate large volumes of data that require careful statistical analysis. Special significance is attached to dose-related trends in the severity of effects, or to effects that are consistent or progressively increase through the generations.

To date, few tests of reproductive toxicity have followed the complete three-generation protocol. Rather, tests in a single generation, often with exposure for a limited period of time, have been performed. Frequently only one sex has been exposed to the test substance.

Dominant Lethal Assay in Mammals

This assay is usually conducted in mice or rats (See Tables V-1 and V-4). Males are treated, usually by intraperitoneal injection, with a series of near-toxic doses of the test agent. Each male is then mated with a number of virgin females each week for 8-12 weeks. Before delivery, the females are sacrificed, and the numbers of live, dead, and resorbed fetuses are counted. The assay is primarily a test for mutagenic effects; dominant lethal mutations are reflected in an increased number of dead or resorbed embryos. Effects on the male may also be reflected in reductions in the total numbers of fetuses.

Other Tests

Table V-1 lists 13 other assay systems that test for possible effects of chemicals on various aspects of reproductive function. Several laboratory tests are available for identifying chemicals or other environmental agents that interfere with spermatogenesis in male animals. Some of these tests are applicable to humans, as well as to laboratory animals. Semen samples from animals or humans can be analyzed for sperm count, motility, and morphology, which may affect fertility in the male (Amelar et al. 1977). Morphologic changes in sperm often reduce their motility. Cytogenetic assessments of spermatogonia, spermatocytes, and oocytes in experimental animals can be used for chromosomal evaluation (Brewen and Preston 1978). Some forms of birth defects (e.g., Down's syndrome) and many spontaneous abortions are associated with chromosomal aberrations (Boue et al. 1975). Hence chemicals that cause chromosomal aberrations in germ cells may present a reproductive hazard. Further, the use of the so-called YFF test, wherein the Y chromosome in the sperm cell can be made visible with fluorescent dye, can be used to assess nondisjunction, which causes sperm to contain an extra Y chromosome. This test may also be used for humans.

A number of toxicologic tests use the male gonads in animals. Since a number of toxic substances have been shown to inhibit testicular DNA synthesis, a test has been devised that measures incorporation of ^{3}H-labeled thymidine as an index of nucleic acid formation in male mice treated with a toxic substance (Friedman

and Staub 1976). Assessment of testicular toxicity can also involve a quantitative analysis of spermatogenesis in both rodent and nonrodent species (Heywood and James 1978). Recently, a canine pituitary-testicular test has been proposed for assessing gonadal function in relation to toxicity evaluation studies (James et al. 1979). Although not always consistently correlated with infertility, increased levels of blood FSH or LH or both can be related to lower-than-normal sperm counts. Sometimes blood hormone levels can assist in establishing the cause as well as the fact of male infertility (Amelar et al. 1977).

Likewise, a number of tests are available for effects on the functioning of the female reproductive system. These include tests for changes in circulating levels of estrogens, prolactin, FSH, and LH (Korenman et al. 1969, Millar and Aehnelt 1977, Monroe et al. 1968). They can be used for humans. Tests for estrogenic effects in animals (usually measured by an increase in uterine weight in ovariectomized animals) are also available (Zarrow et al. 1964). The relationship of these tests to overall reproductive performance is not clear, and they have not been widely used in routine screening. Infertility associated with amenorrhea in humans can be readily assessed.

In Vitro and Other Short-Term Tests

Tables V-2, V-3, and V-4 list a number of short-term assays that measure the effects of chemicals on various cellular and organ systems involved in reproduction. Some of these tests are already in routine use for screening purposes, but most

are in the research stage or have not been used for testing the effects of chemicals. There is considerable doubt about the relevance of these tests for predicting effects on reproductive performance. Nevertheless, many of these tests are simple and inexpensive, and they offer promise for future development as part of a screening system for detecting hazards.

Tests that measure chromosome aberrations in somatic cells are not included in this report. The relationship between the ability of a chemical to cause chromosomal aberrations in somatic cells and in germ cells is not entirely clear and is, in part, a function of toxicokinetics of the chemical; however, such tests might be useful for screening, because a majority of aborted fetuses show chromosomal aberrations (Boue et al. 1975). In fact, any chemical that induces somatic mutations and is capable of reaching sperm or eggs may induce germ cell mutations, which could result in spontaneous abortions, stillbirths, birth defects, or other types of impairment.

General Considerations in Testing

Although some of the assays for specific adverse reproductive effects are quite satisfactory and reproducible, other assays either lack specificity or give inconsistent or variable results. An ideal assessment of reproductive toxicity should be conducted so that it reveals effects on each of the mechanisms leading to fetal abnormality, fetal loss, or damage to offspring in later life. As discussed in Chapter II, there are several stages at which chemicals can adversely affect reproduction:

a. Damage to parental gametes resulting in sterility or abnormal development of the fertilized egg or embryo

b. Interference with normal uterine development and the nutrition of the conceptus

c. Damage to the embryo or inhibition of embryogenesis

d. Toxic effects on the fetus, fetal membrane (yolk sac and amnion), or placenta

e. Inhibition of maternal metabolism causing secondary effects on the fetus

f. Inhibition of uterine growth

g. Adverse effects on parturition

h. Adverse effects on lactation or weaning

i. Latent effects on the progeny, manifested in later life (e.g., as impaired development, infertility, or cancer)

Extensive consideration has been given to optimization of experimental protocols for reproductive toxicity testing. Typical examples of good protocols can be found in the guidelines for assessing reproductive toxicity of chemicals. These guidelines have been published by the U.S. Food and Drug Administration (1970), World Health Organization (1967), Organization for Economic Cooperation and Development (1979), Health and Welfare Canada (1975), the U.S. Environmental Protection Agency (1978), and committees of the National Academy of Sciences (1975, 1977). These bodies have pointed out a number of critical factors involved in the design, conduct, and interpretation of the tests. These factors include:

a. Selection of species

b. Dosage, route, and timing of exposure

c. Number of animals

d. Controls (positive and negative)

e. Toxicokinetics

f. End points

g. Statistical analysis

The selection of the animal species is particularly important, not only for teratology studies, but also for other assays of reproductive effects in females and males. Because one species may prove to be insensitive to a particular chemical, most tests are conducted on at least two species. In selecting the species and strain to be used with a particular chemical, it is important to consider the ability of the animal to mimic the expected concentration and persistence of toxic metabolites at the target tissue in humans. This information may not, however, be available.

Results from reproductive tests may also be influenced by whether the strain is inbred or outbred. Inbred strains show fewer genetically determined differences in individual traits. This allows more precise differentiation of treatment-related effects from spontaneous events. However, two different inbred strains may not respond identically to the same treatment; therefore, the presence or absence of an effect is of limited predictive value to humans. This is also true for outbred strains (Kalter 1978).

The outbred strains are less uniform in their treatment responses between generations. This genetically controlled

variability may more closely resemble the human population, but Kalter (1978) has suggested that the genetic variability of outbred rodents may be less than is usually thought. The greater spontaneous variability in reproductive function in outbred strains will tend to reduce the sensitivity of tests using such strains and may not permit wider generalization or extrapolation of test results.

Despite the analogy between outbred strains and the human population in terms of genetic heterogenicity, proper use of inbred strains may best indicate reproductive effects of a test compound. By using more than one strain and considering the historical control data for each strain, the disadvantages of using inbred strains may be minimized.

Rats, mice, and rabbits have been the most widely used species, for the practical reasons that they are readily available, inexpensive, easy to maintain, and can be bred with relative ease in the laboratory (NAS 1975). Subhuman primates are desirable because of their physiological similarity to humans, but both cost and availability often curtail their use. The adequacy of historical information can be an important consideration in the selection of a test species and strain. The nature and frequency of spontaneous adverse reproductive effects can affect the interpretation of a study.

Dosage is a primary consideration in designing a toxicological test for various effects on the reproductive system. Ordinarily, at least three dose levels are used, in addition to untreated

and vehicle-treated groups (negative controls). Tests are often designed to include at least one dose at a no-effect level and one dose that is overtly toxic to the mothers (but does not kill more than 10% of them) (USEPA 1978, OECD 1979).

In multigeneration reproduction studies with rodents, experiments are designed to assess the effects of chronic exposure to low levels of a chemical on the reproductive capacity of the parents and on the growth and survival of the offspring. When feasible, the chemicals are administered by the likely route for human exposure. Other routes of administration that may yield information about biotransformation of the chemical are sometimes also used.

Some protocols for dosing require administration during critical periods. In the case of teratology experiments, the critical period encompasses organogenesis (see Figure V-1 and Table V-6) when tissue differentation occurs that is specific to the particular species being tested. These protocols could be adapted to study the effects of chemicals on implantation and early embryogenesis before organ formation by altering the time of exposure (e.g., days 4-7 in the mouse). The timing of exposure is critical because exposure at different times during gestation can have different outcomes (see Chapter IV for an example involving anticoagulants).

TABLE V-6

CRITICAL PERIODS OF ORGANOGENESIS IN ANIMALS

Species	Mean Duration of Gestation (days)	Critical Period* (days)
Hamster, golden	16	4-14
Mouse	19	7-16 (6-15)
Rat	21	9-17 (6-15)
Rabbit	31	8-21 (6-18)
Ferret	43	8-28
Cat	63	5-28, with 5-18 most susceptible
Dog	63	1-48, with 8-20 most susceptible
Guinea pig	68	11-20
Pig	114	12-34
Sheep	150	14-36
Rhesus monkey	168	20-45, with 22-30 most susceptible
Baboon	175	22-47
Armadillo	225	1-30
Human	278	20-55
Cow	284	8-25

*Period of embryological organogenesis or period of known susceptibility to teratogens; critical periods for some species estimated by OECD (1979) given in parentheses

Source: Adapted from Schardein 1976, Drugs as Teratogens. CRC Press, Boca Raton, Florida. P 17 (Copyright The Chemical Rubber Co., CRC Press, Inc.). Some estimates from OECD 1979

Experimental protocols to assess adverse effects on the endocrine system ordinarily involve at least a 7-day treatment period, because chemically induced changes in hormone levels usually require this minimum duration of exposure. In mating studies involving treatment of males before insemination of untreated females, adequate time is needed to allow for the development of germ cells to mature sperm. In addition, consideration may be given to whether significant levels of the original chemical (or metabolites) can be detected in the semen. This helps to determine if any adverse effects that are observed are the result of direct effects on sperm or are the result of chemicals transported in semen.

For satisfactory interpretation of experiments involving toxicologic assessments, enough animals must be used to provide statistically meaningful data. The number of animals to be exposed in each dosed group depends on a number of factors, including cost, the required sensitivity of the experiment, the toxicologic effect to be measured, the reproducibility of the effect in the experimental system, and the incidence of spontaneous occurrences of the effect under study. For example, the incidence of spontaneous congenital malformations in animals varies, not only between species, but also between certain strains of rodents. Experimental designs take the rate of spontaneous events into account by ensuring that sufficient numbers of animals are used at each dose level and in the appropriate control groups.

The use of a positive control (an agent known to induce a particular effect or set of effects) is important in teratogenicity testing, because different species and even different strains of rodents differ in their response to teratogens. A positive control group is especially important when a new strain of animals is used or a new test protocol is employed, to ensure that the test system is sensitive to teratogenic effects.

Whenever possible, well-planned reproductive toxicity tests should include the examination of the toxicokinetics of the chemical. The metabolism, distribution, and excretion rates may vary, not only between males and females, but also between pregnant females and their fetuses and between lactating females and their offspring. A chemical having some specific toxic effect on the kidney may reduce its elimination (or metabolism to more polar metabolites) and can exaggerate or aggravate other adverse properties, some of which could lead to endocrine imbalances. Information about blood levels of the toxic agents can substantially contribute to elucidating the chemical's toxicologic profile. Toxic substances that are bound to blood proteins may have a pattern of biodistribution very different from those of chemicals that remain free or unbound in the plasma.

The end points of an experiment are the actual parameters to be assessed following exposure of the test system to a chemical. The more objective an end point is, i.e., the less subjective judgment that is required to determine its presence

or absence, the more reliable the test. If the physiologic-biochemical processes that lead to the end point are fully understood, the evaluation of the effects induced by a toxic agent can be more fully interpreted. Unfortunately, many underlying physiological events in the male and female reproductive systems are not completely understood, and this leads to difficulties in the interpretation of some findings. Some reproductive end points are strongly influenced by several interacting physiological and environmental stimuli, and, because these interactions may be difficult to control, considerable difficulties can arise in the interpretation of test findings. For example, even when the actual end point is reasonably definitive, such as a sperm count, numerous extraneous factors can cause wide fluctuations in control values and hamper the interpretation of test results. For this reason, fluctuations in sperm counts in males that might have been exposed to very low levels of a toxicant are difficult to interpret. Interpretation is further hampered by the fact that the influence of reduced sperm count on reproductive performance is also unclear (see Chapter II).

Reproductive toxicity tests typically require trade-offs between costs and statistical sensitivity. A typical three-generation reproduction test in rodents with three dose levels and 20 litters in each group will involve testing and examining hundreds of litters and thousands of offspring, which must be monitored for many end points. Such an experiment is costly and requires specialists in several biological disciplines.

Nevertheless, the statistical power of such an experiment to detect small effects is limited by the number of litters.

In performing statistical analyses on either teratology or reproduction studies, researchers tend to consider either the litter or the fetus as the experimental unit that potentially could be affected by the treatment. Such approaches do not require difficult statistical techniques, and when effects are pronounced simple statistical techniques may satisfy most criteria for statistical analysis.

However, there has been a great deal of controversy in the field of reproductive toxicology regarding which is the appropriate experimental unit, the entire litter or the individual fetus (Becker 1974; Haseman and Hogan 1975; Kalter 1974; Palmer 1974; Staples and Haseman 1974; Weil 1970, 1974). Looking at the experimental system with the statistical objective of extracting all the information it produces, but not overstating what has been learned, it is clear that, with rare exceptions, neither is really appropriate. In teratology and reproduction studies, the parents are unquestionably the treated unit. However, the effects on the individual fetuses cannot be ignored, because all the fetuses in a litter ordinarily do not respond identically. The degree of response within a litter provides as much and usually more information about the toxic potential of the test substance than does a simple indicator of whether the litter was or was not affected in a certain fashion. Also, because the response within a litter is not likely to be uniform,

the larger the litter (usually considered a sign of reproductive success), the more likely that one or more of its fetuses will be affected with a particular variant characteristic merely by virtue of having more units at risk.

The fetuses in a given litter, however, have more in common with each other than they do with fetuses in another litter of the same treatment group; they are not independent in the statistical sense. They share a more similar genetic constitution with each other than with the offspring of another female. Another level of interrelationship that is usually completely ignored arises in teratology studies by following the common practice of mating groups of two or three females with the same male. The fetuses in different litters sired by the same male have genetic makeups that are more similar to each other than to those of the offspring of another male. Even when inbred strains are used to maximize genetic homogeneity, the fetuses do not respond identically to treatment (Kalter 1965). The fetuses within a litter also share a common maternal environment during gestation (and during lactation, if postnatal observation continues). Such factors would result in the fetuses being positively correlated, that is, reacting similarly. The frequently observed clustering of effects within litters results, at least in part, from these factors.

On the other hand, negative correlation could be postulated on the basis of competition of fetuses within the same litter for maternal resources. Especially in a large litter, the death

of one fetus might increase the chances of survival for the rest.

On the basis of present biological knowledge, it is not possible to predict the exact extent of the maternal or litter effects. Empirical investigations have shown that they do exist (Haseman and Soares 1976). Unfortunately, these studies have also shown that the precise nature of correlation within litters varies from experiment to experiment. Holson et al. (1976) showed that the relative importance of maternal effects can be reduced by increasing the similarity of the females by timing the length of their gestation more accurately. However, the effects due to variable genetics and environment remain from litter to litter.

The existence of correlation, ordinarily positive, means that although each fetus has some information to lend to the statistical analysis, it is not a "full experimental unit's worth." For this reason, counting every fetus as an experimental unit and ignoring litter groupings may artifically inflate the sample size; therefore, the sensitivity of a study is overstated by the less than rigorous application of such statistical methods as chi-square or Fisher's exact tests on individual fetuses. Conversely, if each litter is considered a unit potentially either affected or not affected and so analyzed, the sample size is drastically reduced by a factor corresponding to the average litter size, and all information on degree of response within litters is discarded. Such a statistical approach unjustifiably

restricts the intrinsic power of the gathered data to reveal effects.

Neither the per-litter nor per-fetus interpretation of reproduction data is strictly accurate; most often the truth lies somewhere in between. The results of the two types of analysis may differ greatly. Performing both analyses and drawing a conclusion by consensus is, in effect, testing by litters, and the problem remains of reaching a decision when the outcomes differ in terms of significance. Becker (1974) suggested testing first for maternal effects and then conducting an analysis by fetuses if the maternal effects are not significant and by litter if they are significant. This is an improvement, but it too lacks precision. Another intermediate approach, which is quite often used, is to calculate the average of a particular effect over the litters of a treatment group and to treat the resulting mean as an approximately normal variable to be compared with the control group using the t-test or, more conservatively, the nonparametric Mann-Whitney test. The sample size is reduced to the number of litters, yet a measure of degree of effect is retained. However, if the theoretical binomial variance, rather than the sample variance among the litters, is used for dichotomous variables or if the simple sample variance among the litter averages is used for continuous variables, all information about the variable's distribution in the sample has not been used.

A second great difficulty in the analysis of litter data arises because litters vary in size. A small litter does not contain as much information as a larger one and cannot be used to estimate an incidence rate as accurately. For instance, if the underlying "true" incidence of an experimental end point is 50%, a litter of four fetuses can respond as 0, 25, 50, 75, or 100% affected and can be expected to have these outcomes 6.25, 25, 37.5, 25, and 6.25% of the time, respectively. A litter that is twice as big could respond as 0, 12.5, 25, 37.5, 50, 62.5, 75, 87.5, or 100% affected and would be expected to have these outcomes 0.4, 3.1, 10.9, 21.9, 27.3, 21.9, 10.9, 3.1, and 0.4% of the time, respectively. These latter responses can be seen to cluster more closely about the "true" value of 50%; the variance of the estimate of incidence given by the larger litter is smaller. For this reason, a result from a larger litter would be regarded with more confidence. It should therefore be entered into a combined estimate, an average over litters, with more weight. Gladen (1979) has suggested a "jack-knife" procedure to accomplish this when averaging over litters before testing with a t-statistic.

Theoretically, it would be most desirable to analyze teratological or reproductive data by a method that corresponds to a mathematical model describing the biological system very exactly (Haseman and Kupper 1979). Such a model should be tested empirically on existing data to see if it actually fits well. What are known as "nested designs" with random effects seem

most natural to statisticians who have considered this problem. This type of model leads to an analysis of variance in which the within-litter variability is compared to the between-litters variability in order to derive an accurate estimate of variance for comparison of the treatment means. The various models that have been developed--beta-binomial (Williams 1975), negative binomial (McCaughran and Arnold 1976), and correlated binomial (Altham 1978, Kupper and Haseman 1978)--are characterized within this basic framework by the type of interaction assumed between the fetuses of a litter. Although it fits actual data well, the negative binomial model can be faulted because, being based on Poisson counts, it does not take litter size into account. For analysis of future work, the beta-binomial or correlated binomial model are highly recommended for the most efficient extraction of the information the experimental effort has generated.

VI. CONCORDANCE BETWEEN REPORTED EFFECTS IN HUMANS AND MEASURED EFFECTS IN ANIMALS

The experimental assays that have been described in Chapter V are conducted generally for two purposes: (a) to investigate mechanisms of action of toxic chemicals on various reproductive processes; or (b) to screen chemicals in order to identify those that may present hazards to humans exposed to them. In fact, three of the assays--the teratogenicity test, the three-generation reproduction test, and the dominant lethal assay in mammals--are used routinely to screen such chemicals as drugs and pesticides to establish their safety prior to clinical trials or commercial production. This chapter presents a brief discussion of the scientific basis for the use of animal test results. Specifically, we explore the problem of extrapolating reproductive toxicity data in animals to predict human risks. Ultimately our ability to use the results of animal studies will depend on our ability to establish their predictive power. To do so, we need to establish the degree of concordance between the responses of humans and animals to a representative range of chemicals. If this concordance is found to be close for the chemicals for which data are already available, it will be reasonable to assume that it will remain close for other chemicals. On the other hand, if marked differences are found, it will be difficult to predict likely human responses. Together with knowledge of biological similarities and differences,

empirical evidence of concordance provides the theoretical basis for using animal test data to predict hazard (or lack of hazard) to humans.

"Concordance" between the effects of chemicals in humans and in experimental animals has two major components: concordance of effect and concordance of dose. Concordance of effect is the extent to which the types of effects observed in humans are matched by similar or related effects observed in animals. For example, if an agent is known to be teratogenic in humans, is this effect matched in animals by teratogenic effects or by other effects on the fetus? If it is teratogenic in animals also, are the same organs affected? An important consideration is the concordance of effects among the various animal species that are used in laboratory experiments. If a chemical agent gives rise to the same kind of effect in all animal species that are tested, then it is easy to know which effect is to be predicted in humans. On the other hand, if the effects observed in different animal species differ widely, it is impossible to make predictions unless there is some reason to select one species as more likely to be predictive than others.

Concordance of dose is the extent to which humans and animals are affected at similar dose levels. Again it is important to examine whether there is concordance of dose among the animal species that have been tested. If there is wide variation in effective doses in different species, primary attention should be paid to the most sensitive species, because

the results in this species will suggest the likelihood of responses in humans at the lowest doses.

Although human experience is ultimately necessary to confirm or refute the results of predictions derived from the results of animal tests, screening tests in animals are necessary for several reasons:

1. Experimental studies that involve deliberate exposure of humans to potentially toxic chemicals are ethically unacceptable except in special circumstances (e.g., clinical trials of new drugs for which there is already extensive evidence of safety from animal experiments).

2. Nonexperimental studies in humans (e.g., studies of workers exposed to a chemical already in production or reports of adverse reactions to drugs) are available for only a small number of chemicals (see Chapter IV).

3. Even when studies of exposed human populations can be carried out, it is difficult to follow ideal designs and to investigate all effects of interest, because of the difficulty in measuring reproductive impairment levels of exposure. The interpretation of such studies is often hampered by confounding factors, such as smoking habits and exposure to other chemicals.

4. Although positive evidence of effects may be fairly easy to establish in some circumstances, satisfactory evidence for lack of effect is impossible to obtain unless extremely large studies are conducted. Even in ideal circumstances (a well-controlled study, with documentation of confounding factors,

in which the effect produced is rare or conspicuous), the smallest number of excess cases that could be detected with statistical confidence is three or four. If the effect produced is an increase in a frequent condition, such as spontaneous abortion or low birth weight, the smallest number of excess cases that could be detected with statistical confidence may be 10, 20, or more, depending on the circumstances. Even if 1,000 persons were studied, a negative result would mean only that the excess incidence of adverse effects attributable to the agent is not more than about 1%. A negative result in a study of 10,000 persons similarly gives an upper limit of about 1 per 1,000 for the excess incidence of effects.

Thus, although more epidemiological studies of persons exposed to potential reproductive hazards will be extremely valuable, preliminary tests in animals will usually be the primary source of data, from which human risk and safety must be assessed.

A basic assumption in toxicology is that effects observed in experimental animals can be used to infer likely effects (or lack of effects) in humans, with appropriate consideration of the biological differences between species. However, it is frequently difficult to take such differences into account appropriately. Reproductive processes in humans are broadly similar to those in the mammalian species--mouse, rat, hamster, guinea pig, rabbit, dog, and rhesus monkey--that are used in screening tests. However, there are a number of differences

in anatomy, physiology, and timing of exposure that need to be taken into account when interpreting experimental results. For example, the critical periods for organogenesis are characteristic of each species (Nishimura and Shiota 1977; see Table V-5). There are substantial interspecies differences in the structure of the placenta; more tissues separate fetal and maternal blood in women and female primates of other species than in rodents and rabbits, but dogs and some other species have even more tissues (Table VI-1). Humans are also known to differ from some of the experimental species in timing of development of the placenta and in other aspects of placentation (Nishimura and Shiota 1977), and in metabolism and pharmacokinetics of toxic chemicals (Gillette 1977). Moreover, humans live in a much more complex environment than the environment of experimental animals and are subject to periodic stresses of various kinds, including concomitant exposure to a wide variety of drugs and environmental chemicals.

A list of factors to be taken into account in extrapolating teratologic data in animals to humans has recently been presented by the Food and Drug Administration (USFDA 1980):

> Interpretation of the relevance of teratology studies to human is affected by many considerations, which combine to make the interpretation of teratology studies complex, difficult, and uncertain (Ref. 33). These considerations, which are the same whenever one attempts to extrapolate from an observed teratologic response in one species to what might be expected to occur in another, include:
>
> 1. Physiological and biochemical differences that affect the absorption, metabolism, and excretion of the substance.

TABLE VI-1

TISSUES SEPARATING FETAL AND MATERNAL BLOOD

	Maternal Tissue			Fetal Tissue			
	Endothelium	Connective Tissue	Epithelium	Trophoblast	Connective Tissue	Endothelium	
Epitheliochorial	+	+	+	+	+	+	Pig, horse, donkey
Syndesmochorial	+	+	-	+	+	+	Sheep, goat, cow
Endotheliochorial	+	-	-	+	+	+	Cat, dog
Hemochorial	-	-	-	+	+	+	Woman, monkey
Hemoendothelial	-	-	-	-	-	+	Rat, rabbit, guinea pig

Source: Adapted from Doull, Klaassen, and Amdur 1980, Casaretts and Doull's Toxicology: The Basic Science of Poisons. Macmillan Publishing Co., New York. P 42 (Copyright Macmillan Publishing Co., Inc.)

2. Variability in placental barriers.

3. Differences in susceptibility to chemical interactions at the cell, tissue, organ, and organ system levels.

4. Variability in background incidence of disease.

5. Variability in the gestational development sequence.

These factors must be taken into account, to the extent the available data permit, when one attempts to assess the relevance to humans of any specific teratology study conducted in a particular species on a particular chemical.

(45 F.R. 69823, citing Wilson and Fraser 1977a)

For these and other reasons, it is impossible to establish a priori what differences are to be expected between the responses of humans and other mammalian species to agents that may affect reproduction. Ultimately, the degree of concordance between human and animal responses must be established by observation, using the data for the sample of chemical agents for which adequate comparative data are available.

Although the empirical correlation between human and animal responses to certain teratogenic agents has been discussed by several authors (Wilson 1977, Wilson and Fraser 1977a, Nishimura and Shiota 1977, Schardein 1976, USFDA 1980), very little discussion of this correlation for other types of reproductive impairment has been published. In the remainder of this chapter, we summarize and extend the findings of other authors with regard to teratogenicity, add a comparison of effective doses of teratogenic agents in humans and animals, and present a preliminary study of the correlation for other types of effect. A more

detailed study of these and other questions involved in the use of animal data is now being conducted by the Interagency Regulatory Liaison Group (IRLG 1980).

As the basis for the comparisons in this chapter, we have tabulated in Appendix A the results of studies of the effects of 21 selected agents on reproduction in humans and in experimental animals. The agents were selected to represent a wide range of types of chemical and conditions of exposure, including therapeutic drugs, cigarette smoking, alcohol consumption, occupational factors, and environmental pollutants. The sources of information for effects on humans are those cited in Chapter IV and Appendix A; for effects on animals, readily available published sources were used, including review papers where appropriate.

This analysis is limited to agents for which human responses have already been recognized. Hence it may be biased towards chemicals to which humans are especially sensitive. The problem of identifying "false positives" (i.e., chemicals that cause teratogenic or other reproductive effects in animals, but for which there is little or no evidence of effects in humans) is discussed later in the chapter.

Concordance of Effects for Teratogenic Agents

Several authors have pointed out that each of the major classes of drugs known to be teratogenic in humans has similar effects in at least some animal species.

> Steroid hormones with androgen activity have produced pseudohermaphroditism in female fetuses in a number of species. Aminopterin is teratogenic in rats,

> sheep, dogs, and pigs, and methotrexate is an active teratogen in a variety of species. Similarly, most of the antithyroid agents induce thyroid defects, along with other anomalies, in a number of species. Thalidomide, despite its profound teratogenic effect in humans, is markedly less potent in laboratory animals. To date, in approximately 10 strains of rats, 15 strains of mice, 11 breeds of rabbits, 2 breeds of dogs, 3 strains of hamsters, 8 species of primates, and in such other varied species as cats, armadillos, guinea pigs, swine, and ferrets in which thalidomide has been tested, teratogenic effects have been induced only occasionally. Effects similar to the phocomelic-type limb deformities observed in man have been produced consistently in only a few breeds of rabbits and in seven species of primates.... (Schardein 1976, Drugs as Teratogens. CRC Press, Boca Raton, Florida. P 5 (Copyright The Chemical Rubber Co., CRC Press, Inc.))

A similar qualitative agreement is found for diethylstilbestrol, which has induced abnormalities of the genital tract in mice, rats, and rhesus monkeys (See Appendix A).

Table VI-2 summarizes data on 10 other teratogenic agents. With two exceptions, there are close parallels in the results of the animal experiments to the effects reported in humans. The exceptions are anesthetic gases (for which the human findings were limited to soft-tissue abnormalities that probably would not have been detected in the animals), and warfarin (for which there have been several case reports in humans, but negative studies in mice and rabbits). Busulfan may also be an exception, but the human evidence for this chemical is limited to one case report. In the case of polychlorinated biphenyls, effects similar to those observed in humans were seen only in rhesus monkeys, dogs, and swine: no teratogenic effects were seen in rats. (The data on polychlorinated biphenyls are complicated

TABLE VI-2

COMPARISON OF REPORTED TERATOGENIC EFFECTS
OF 10 AGENTS IN HUMANS AND IN EXPERIMENTAL ANIMALS

(Condensed from data in Appendix A)

Agent	Reported Sites In Humans	Reported Sites In Animals
Anesthetic gases	Hemangiomas, hernias, skin, heart	Skeletal defects only: rat, mouse (halothane and N_2O)
Smelter emissions (lead and/or arsenic)	Multiple malformations	Multiple malformations: rat, mouse, hamster (lead and arsenic)
Polychlorinated biphenyls	Skin discoloration; enlarged fontanelles	Skin discoloration and lesions rhesus monkey; enlarged fontanelles and syndactyly; pig, dog; negative: rat, rabbit
Alcohol	Facial, CNS	Facial, dermal, neural, extremities: rat, mouse
Vinyl chloride	Neural tube?	Various, including encephalocele: rat
Warfarin	Nose, bones (case reports only)	Negative: mouse, rabbit
Diphenyl-hydantoin	Cleft lip, cleft palate, other craniofacial, mental deficiency	Cleft lip, cleft palate, syndactyly, other skeletal defects: mouse; minor kidney anomalies: rhesus monkey

TABLE VI-2 (continued)

Agent	Reported Sites In Humans	Reported Sites In Animals
Aminopterin	Multiple malformations	Multiple malformations: sheep, rat
Busulfan	Eye, cleft palate (1 report)	Skeletal, genital defects: rat
Methotrexate	Skull, ribs, toes (2 reports)	Various: rat, cat, rabbit, mouse
Methylmercury	CNS	CNS, skeletal: rat, mouse, hamster, cat

by simultaneous exposure to toxic impurities.) In other cases, effects observed in rats were qualitatively similar to the effects observed in humans.

A parallel but more extensive comparison of human and animal responses to teratogenic agents has recently been published by the Food and Drug Administration (USFDA 1980):

> In an effort to better understand as a general matter the relevance of animal teratology studies to humans, several investigators have examined the literature to determine the extent to which known or suspected human teratogens have also been found to be teratogenic in animals (Refs. 34, 35, 36). FDA's review of the literature reveals a group of 38 compounds for which there are reports of birth defects in humans associated with intake of these compounds during pregnancy (Refs. 36, 37, 38, 39). Of these compounds, all except one have a positive study in at least one animal test species. Furthermore, over 80 percent of the compounds are positive in multiple species. The one exception is a compound that causes otological deficits in humans that would not normally be discovered in test animals at the time of caesarian sacrifice.
>
> Among the most widely tested individual species, a positive teratologic response to the substances identified as known or suspected human teratogens was exhibited 85 percent of the time in the mouse, 80 percent in the rat, 60 percent in the rabbit, 45 percent in the hamster, and only 30 percent in the monkey. Other species have been used to test only a small number of these substances. Nevertheless, there has been a greater than 80 percent correlation with the positive human data for the dog, pig, cow, and cat.
>
> 45 F.R. 69823, citing Wilson 1973b, Schardein 1976, Strobino et. al. 1978, U.S. Pharmacopeia 1980, and compilations of other data

These results suggest that teratogenic effects of chemicals observed in humans are likely to be matched in most cases by

effects in other species, provided that appropriate species can be selected in each case. However, the results summarized in Table VI-2 and by the Food and Drug Administration (USFDA 1980) make it clear that no single species will suffice to predict effects in humans. Schardein (1976) has also given an extensive discussion of interspecies variations in susceptibility to teratogens. The experience with thalidomide illustrates dramatically that tests in one or even several small animal species may give "false negative" results for a chemical to which humans are especially sensitive.

Thus, although retrospective analysis of the data on these 10 chemicals shows close concordance of effect, in fact the serious damage caused by thalidomide was not predicted, because the more predictive species had not been tested.

Concordance of Dose for Teratogenic Agents

Table VI-3 compares the lowest effective teratogenic dose of thalidomide recorded in humans with those recorded in a variety of other species. Humans appear to be about as sensitive to thalidomide as the most sensitive species tested (the cat), and they are 5-10 times more sensitive than the species that showed similar patterns of defects (the rabbit and various monkey species).

Table VI-4 contains data on the lowest effective doses for thalidomide and for seven other agents that have been reported to have teratogenic effects in humans. (Data on busulfan are not used in this comparison, because the human data are

TABLE VI-3

COMPARISON OF DOSES REQUIRED FOR TERATOGENIC EFFECTS OF THALIDOMIDE IN VARIOUS MAMMALIAN SPECIES

Species	Lowest Dose (mg/kg) For Detectable Effects
Human	0.5-1.0
Monkey	10
Rabbit	2.5
Mouse	31
Rat	10
Armadillo	100
Dog	100
Hamster	350
Cat	0.5

Source: Adapted from Schardein 1976, Drugs as Teratogens. CRC Press, Boca Raton, Florida. P 6 (Copyright The Chemical Rubber Co., CRC Press, Inc.)

TABLE VI-4

COMPARISON OF LOWEST EFFECTIVE DOSES
OF EIGHT TERATOGENS IN HUMANS AND ANIMALS

(Condensed from data in Appendix A)

Chemical	Lowest Effective Dose In Humans	Lowest Effective Dose In Animals	Species	Ratio of Animal Dose: Human Dose
Thalidomide	0.5-1.0 mg/kg/d (a)	2.5 mg/kg/d (a)	Rabbit	5-2.5
Polychlorinated biphenyls**	70 µg/kg/d (b)	125 µg/kg/d (c)	Rhesus monkey	1.8
		1,000 µg/kg/d (d)	Dog	14.3
Alcohol	0.4-0.8 g/kg/d (e)	1.5 g/kg/d (f)	Rat	3.8-7.6
Aminopterin	50 µg/kg/d (g)	100 µg/kg/d (h)	Rat	2
Methotrexate	42 µg/kg/d (i)	200 µg/kg/d (j)	Rat	4.8
Methylmercury*	5 µg/kg/d (k)	250 µg/kg/d (l,m)	Cat, rat	50
DES	20-80 µg/kg/d (n)	200 µg/kg/d (o)	Rhesus monkey	10-2.5
Diphenyl-hydantoin	2 mg/kg/d (p)	50 mg/kg/d (q)	Mouse	25

*For blood levels of 200-500 ng/ml, the equivalent long-term daily intake of mercury as methylmercury is 3-7 µg/kg/day (NRC 1978).

**and/or polychlorinated dibenzofurans

References indicated by letters in parentheses are listed on next page.

References for Table VI-4

a. Schardein 1976

b. Kuratsune et al. 1972

c. Allen and Barsotti 1976

d. Earl et al. 1976

e. Hanson et al. 1978

f. Sandor and Amels 1971

g. Emerson 1962

h. Baronov 1966

i. Milunsky et al. 1968

j. Wilson 1971

k. Amin-Zaki et al. 1976

l. Khera 1973a,b

m. Khera and Tabacova 1973

n. IARC 1979

o. Hendricks 1979

p. Hanson and Smith 1975

q. Harbison and Becker 1969

limited to one case report and different types of defects were included in animals.) The doses tabulated are the lowest doses reported (in the studies cited in Appendix A) to be associated with teratogenic effects in humans and in the most sensitive species of mammals tested. Data are limited to the cases in which the effect reported in animals was similar to that reported in humans. To permit direct comparisons, doses are converted to units of weight per unit body weight per day.

Table VI-4 shows that, when doses are expressed in these units, effective doses for animals are in all cases greater than those for humans, by factors between 1.8 and 50. That is, humans are more sensitive than the most sensitive experimental animals tested to date, by factors in this range. If doses were expressed as weight per unit surface area per day, another common way to compare doses between species, the ratios between lowest effective doses in animals and in humans would lie in the range of 0.3-8.

A more detailed comparison between effective doses would take into account the timing and duration of dosage, the magnitude of the responses in both humans and animals, the pharmacokinetics of the chemicals in the various species, and differences in response between the various animal species. However, the simple comparisons presented in Table VI-4 indicate reasonably close concordance of dose. An assumption that humans are likely to be 10 times more sensitive than the most sensitive species of mammal, for example, would predict the lowest effective human

dose in all cases within a factor of 6. At the least, this analysis suggests that the data on these and other human teratogens should be studied more intensively, to confirm or refute these preliminary results.

Concordance of Effect for Agents Other Than Teratogens

It is more difficult to make detailed comparisons between humans and experimental animals for effects on reproduction other than teratogenesis. The principal difficulty is that many different end points have been recorded in both humans and animals. It is not always clear that effects recorded in experimental animals would have been detected in humans, or vice versa. In some cases the same effect would be recorded as a different end point in humans and animals: for example, embryonic death would generally be recorded (if at all) as spontaneous abortion in humans, but as resorption or reduced litter size in animals. For several chemicals, the only effects recorded in humans were birth defects, or effects that were not looked for in animals.

Despite these difficulties, it is possible to compare the effects for at least 10 of the 21 agents included in Appendix A. The following summary shows that there is a good general concordance between the recorded effects where the observations overlap.

Anesthetic gases. The most consistent observation in humans, increased frequency of spontaneous abortion in exposed females, was matched by an increased frequency of resorptions in hamsters and rats exposed to halothane and nitrous oxide.

Lead. The wide spectrum of effects associated with exposure of both males and females was matched by a similarly wide spectrum of effects resulting from exposure of both sexes of rats and mice.

Polychlorinated biphenyls (PCBs). The menstrual disturbance reported in exposed women was matched by disruption of estrus in both rhesus monkeys and mice. Spontaneous abortions were conspicuous in rhesus monkeys, but apparently not in the exposed women.

Alcohol. Reduced birth weights in humans were matched by reduced birth weights in guinea pigs and rats. Fetal deaths were recorded in several animal species, and some evidence points to spontaneous abortions; effects noted in humans included reduced birth weight, spontaneous abortions, and stillbirths.

Ethylene dibromide. Apparent reduction in fertility in exposed men was matched by sterility in exposed rats and bulls.

Kepone. Infertility and loss of sperm motility in exposed men was matched by a reduction in the sizes of litters sired by exposed male mice. The animal data suggested that females were affected more than males by kepone, but no women appear to have been heavily exposed to this chemical during manufacture.

Carbon disulfide. Sperm abnormalities in exposed men were matched by effects on spermatogenesis in rats. Spontaneous abortions in exposed women were matched by early embryonic mortality in exposed rats, but in that species congenital malformations also were frequent.

Dibromochloropropane (DBCP). Decreased or zero sperm counts in exposed men were matched by atrophy and degeneration of the testes in exposed rats, rabbits, and guinea pigs.

Aminopterin. Spontaneous abortion, the most frequent effect in treated women, was matched by abortion in macaque monkeys and resorptions or embryolethality in rats.

Diethylstilbestrol (DES). Spontaneous abortion in some treated women was matched by spontaneous abortion in treated rabbits.

Although it is difficult to make a rigorous comparison of such diverse and unsystematic data, the above summary suggests a generally close concordance between the effects of these 10 chemicals in humans and in experimental animals. At least some of the divergences may be attributable to differences in dosage and circumstances of exposure.

Concordance of Dose for Agents Other Than Teratogens

The studies summarized in Appendix A include only eight cases in which the doses associated with recorded effects in humans can be compared with the doses that induced similar effects in animals. These cases are tabulated in Table VI-5; the same methods were used for selecting and presenting data as those used for Table VI-4. If doses are expressed in units of weight per unit body weight per day, the ratios between the lowest effective doses in animals and in humans range between 0.4 and 25. If doses are expressed in units of weight per unit surface area per day, these ratios range between 0.06 and 4.5. For

TABLE VI-5

COMPARISON OF DOSES AT WHICH NONTERATOGENIC EFFECTS OF SELECTED CHEMICALS WERE RECORDED IN HUMANS AND ANIMALS

Chemical	Effect in Humans	Lowest Dose or Concentration Reported	Animal Species	Effect in Animals	Lowest Dose or Concentration Reported	Ratio of Animal Dose: Human Dose
Polychlorinated biphenyls	Menstrual disturbance (a)	70 µg/kg/d	Rhesus monkey	Abortion, infertility, menstrual disturbance (b, c)	125 µg/kg/d	1.8
Alcohol	Spontaneous abortion (d)	0.1 g/kg/d	Mouse	Fetal death	6 g/kg/d	60
			Dog	Spontaneous abortion (e, f)	4 g/kg/d	40
			Guinea pig	Reduced birth weight (g)	2.5 g/kg/d	25
Ethylene dibromide	Reduced fertility (males) (h)	Up to 6 mg/kg/d	Rat	Unsuccessful mating (males) (i)	53 mg/kg/d (no effect at 23 mg/kg/d)	8.8
Carbon disulfide	Sperm abnormalities (j)	7-14 mg/kg/d	Rat	Testicular damage, no spermatogenesis (k)	39 mg/kg/d	5.5-2.7
Carbon disulfide	Spontaneous abortions, premature births, menstrual disturbance (l, m)	1.5-4.5 mg/kg/d	Rat	Decreased organ-to-body weight ratio and nervous system disfunction in offspring (n)	0.6 mg/kg/d*	0.4-0.1

*There may be effects at a lower dose, as suggested in the English summary to this Russian paper, but our translation of the article did not confirm this.

TABLE VI-5 (continued)

Chemical	Effect in Humans	Lowest Dose or Concentration Reported	Animal Species	Effect in Animals	Lowest Dose or Concentration Reported	Ratio of Animal Dose: Human Dose
Dibromo-chloro-propane	Sterility, reduced sperm counts (o)	0.5 mg/kg/d	Rat	Atrophy and degeneration of testes (p)	9 mg/kg/d	18
Aminopterin	Abortion (q)	50 µg/kg/d	Macaque monkey	Abortion (r)	100 µg/kg/d	2
Hexachloro-benzene	Infant mortality, stillbirths (s, t)	1-4 mg/kg/d	Rat	Stillbirths, postnatal mortality, reduced birth weight (u)	4-8 mg/kg/d	4-2

Notes:

Exposure information for some chemicals was not in terms of dose/unit body weight/day. When necessary, the following assumptions were made to calculate the dosage in ug, mg, or g/kg/d: The body weight of a human is 60 kg; a monkey weighs 5 kg and consumes 250 g of food/day; a rat weighs 0.4 kg and consumes 20 g of food/day. Alcohol has a density of 0.8 g/ml; quantities expressed in ounces are fluid volumes. Occupational exposure is 8 hours/days; 10 m^3 of air are inhaled in an 8-hour work day, and no inhaled chemical is lost by exhalation.

References indicated by letters in parentheses are listed on next page.

Reference for Table VI-5

a. Kuratsune et al. 1976

b. Allen et al. 1976

c. Allen and Barsotti 1976

d. Kline et al. 1980d

e. Kronick 1976

f. Ellis and Pick 1976

g. Papara-Nicholson and Telford 1952

h. Wong et al. 1979

i. Short et al. 1979

j. Lancranjan 1969

k. Gondzik 1971

l. Vasilyeva 1973

m. Petrov 1969

n. Sarnikova and Chirkova 1976

o. Whorton et al. 1976

p. Torkelson et al. 1961

q. Emerson 1962

r. Delahunt 1966

s. Peters 1976

t. Courtney 1979

u. Grant et al. 1974

seven of the eight cases, the latter ratios lie between 0.63 and 4.5. The exception is carbon disulfide, to which female rats were reported to respond to lower doses than women, although the paper reporting this effect provided insufficient evidence for evaluation.

For the limited number of examples in Table VI-5, there seems to be a general concordance between effective doses in humans and animals for reproductive effects other than teratogenesis, but this concordance appears to break down in at least one case. There needs to be a more detailed analysis of these data, which includes consideration of dose-response data, timing of dosage, pharmacokinetics, and species differences.

Concordance of "Nonpositive" Data

The foregoing analysis of the concordance between effects of chemical agents in humans and in experimental animals has necessarily been limited to agents that are known to affect humans. The Food and Drug Administration (USFDA 1980) has attempted also to investigate the degree of concordance between animal test results and human experience for agents that are not known to be teratogenic in humans.

> The correlations between human response and the responses of specific species are not as good for the compounds that do not appear to be human teratogens. Of the 165 compounds for which human teratologic effects have not been reported, 28 percent appeared negative in all animal species tested and 50 percent appeared negative in multiple species. However, 41 percent of these 165 compounds appeared to be positive in more than a single animal species. For the most commonly tested species, a non-positve

> response to the substances for which human teratologic effects have not been reported was observed 80 percent of the time for the monkey, 70 percent for the rabbit, but only 50 percent for the rat, 35 percent for the mouse, and 35 percent for the hamster.
>
> 45 F.R. 69823

However, as FDA pointed out (p. 69824), these conclusions are limited by the inconclusiveness of some of the data suggesting lack of teratogenicity in humans. In fact, as pointed out earlier, studies in humans can only set an upper limit on the possible frequency of effects; they cannot in principle prove that no effect takes place. Thus, although the Food and Drug Administration has identified 67 chemicals that appear to be teratogenic in more than one animal species but "do not appear to be teratogenic in humans," the evidence for the latter conclusion is relatively weak and is likely to remain so.

This problem is of great practical significance, because a very large number of chemicals is known to cause adverse effects on reproduction in animals. Of 1,930 drugs that have been tested for teratogenicity in animals, about one-third have yielded positive results, including such common drugs as aspirin, penicillin, and cortisone (Schardein 1976, Wilson 1973b). All heavy metals and a large fraction of pesticides are known to cause adverse effects on reproduction in animals (Wilson 1977). Although there is little evidence to link these agents with actual effects in humans exposed to them, direct studies in humans are unlikely to confirm or refute the possibility that small effects may be taking place. For this reason, it is impossible to know

whether a positive result reported in animals indicates that a chemical actually would pose hazards to humans exposed to sufficiently large quantities.

The case of caffeine provides a good illustration of the problem. A recent teratology study in rats indicated that caffeine induced irreversible terata at doses as low as 80 mg/kg/day, and other adverse, but probably reversible, effects at doses as low as 6 mg/kg/day (USFDA 1980). These doses are close to typical daily intakes in the human population (2 cups of coffee is equivalent to an intake of about 6 mg/kg). Although six epidemiologic studies have investigated possible teratogenic effecs of caffeine in humans, these studies were generally "flawed by a failure to control important variables that could alter study results" and were therefore regarded collectively as inconclusive (USFDA 1980). The relevance of the rat data for prediction of human risk is questionable, because rats and humans appear to metabolize caffeine differently. The Food and Drug Administration is requiring additional studies that may help to resolve these issues.

Dose-Response Relationships

Very little appears to have been published on dose-response relationships for agents that affect reproduction in humans, although such relationships could probably be constructed from the data collected on the effects of alcohol consumption and cigarette smoking. Teratologists have usually assumed that teratogenic agents have a threshold dose below which no effects

can be demonstrated (NAS 1975). The basis for this assumption is both empirical, in the observation that measured dose-response curves usually rise steeply once the dose required to show the first effect is exceeded, and theoretical, in the hypothesis that birth defects occur when a critical number of cells in a population destined to form a tissue, organ, or organism is damaged (Wilson and Fraser 1977a).

It is not clear whether these arguments can be used to predict the shape of dose-response relationships in human populations. The theoretical reasons for expecting a threshold dose in a single animal or a small, homogeneous group of test animals are not necessarily applicable to a large, diverse population. In such a population, a "dose-response relationship" is a measure of the frequency distribution of individual thresholds, and this may be very wide if the population is diverse. The assumption that a threshold will exist for an entire population is equivalent to the assumption that there are no individuals in the population whose thresholds are close to zero. The latter assumption is unlikely to be valid if the agent under consideration acts to increase the probability of occurrence of a type of defect that already exists in the population. This may occur, for example, if the agent acts in combination with other environmental agents (Manson 1978).

Conclusions

After reviewing data on the teratologic potential of 203 chemicals, the Food and Drug Administration (USFDA 1980) drew the following conclusions:

> In conclusion, it is reasonable to conclude that positive animal teratology studies are at least suggestive of potential human response. Well-conducted animal studies that show teratogenic effects at levels of exposure not substantially greater than humans might experience are sufficient to raise substantial questions about the potential risk to humans. However, at this time, no single test species can be said to predict accurately the true human response to a given chemical. Tests in multiple species may increase the predictive reliability of animal test data, but specific differences between the test species and the human system must by considered in evaluating the relevance of particular tests to humans....
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The results of the analysis reported in this chapter are consistent with these conclusions and extend them in several ways. For a smaller sample of agents, they show that teratogenic effects in humans are matched by teratogenic effects in one or more species of experimental animal, and are also matched by effects at similar sites in at least one species. They suggest further that there may be fairly close concordance in the dose levels at which humans and animals respond to these agents, humans appearing somewhat more susceptible than the most sensitive animal species tested. In addition, this analysis suggests that there may be similar concordance between humans and animals for other types of effects on reproduction, although in at least one case an animal species appeared to be much more sensitive than humans.

These conclusions, however, are subject to three important qualifications, all of which were pointed out by the Food and Drug Administration at the conclusion of its analysis. First, the human data on the various agents studied are of widely varying quality and quantity. It is possible, therefore, that additional study will modify the conclusions that have been drawn in this analysis. Second, there are marked differences in the response of different animals species to several agents. It is evident that no single species will suffice to predict human response, and it is not clear a priori which species is likely to be most predictive in any particular case. Third, many chemicals known to affect reproduction in animals are not known to do so in humans. With the information now available, it cannot be determined whether the lack of positive findings in humans in these cases is due to the absence of human response to these agents, to low susceptibility of humans, to lack of sufficient human exposure, or to inadequate study.

These uncertainties make it very difficult to evaluate the reliability of animal experiments as predictors of human hazard (or lack of hazard). A predictive system based on animal tests would probably have to include several different animal species. However, without detailed knowledge of comparative metabolism and pharmacokinetics, it will be difficult to decide which species should be used in any particular case. Such a system may generate an unknown number of "false positive" predictions of hazard. Resolution of these problems will require

more intensive epidemiologic studies and further research in comparative toxicology.

VII. POLICY ISSUES RAISED BY THIS REPORT

A number of policy issues are raised by the information reviewed and summarized in this report. These issues are listed and briefly described in this section. Although the relevance of the material in the report to each issue is pointed out, no attempt is made to resolve these issues or to make recommendations for action (other than further research).

How Important is Reproductive Impairment as a Public Health Problem?

Reproductive impairments of one kind or another are frequent and widespread in the U.S. population (Chapter II). Birth defects are generally regarded as the most important part of this public health problem, because of the large economic and psychological burdens they impose on parents and on society. However, inability to conceive, spontaneous abortions, premature births, low birth weight, and perinatal mortality affect millions of couples at one time or another. The overall burden placed on society by reproductive impairments has not been assessed comprehensively.

Do Chemicals Play an Important Role in Reproductive Impairments?

The evidence reviewed in this report is insufficient to assess the importance of the role played by chemicals in reproductive impairments in the U.S. population. At least two agents appear to have substantial effects, but data on others are generally fragmentary and incomplete (Chapter IV). At the

least, these data suggest that a greater research effort is needed to provide answers to this potentially important question.

How Good is the Screening System for Identifying Chemical Hazards to Reproduction?

Chemical hazards to reproduction may be identified either by study of exposed human populations or by laboratory tests. Existing surveillance systems have not yet proved useful in identifying hazards, and need improvement and extension if they are to be so (Chapter III). Despite problems in conducting them, epidemiological studies of exposed groups have been effective in identifying a number of reproductive hazards; more studies are needed (Chapter IV). A number of laboratory tests for reproductive toxicity are available, but they are expensive to conduct and have only been applied systematically to limited classes of chemicals. Further development of test systems is needed, in particular the development of rapid prescreening tests (Chapter V). Although there is encouraging concordance between the results of human studies and animal tests for some agents, the reliability of animal screening systems as predictors of human hazard is not yet established (Chapter VI). More study and assessment are needed in all these areas.

Can the Magnitude of Human Risks be Assessed?

Except where effects in humans at exposure levels of interest can be measured directly by epidemiologic methods, there appear to be no accepted methods for assessing all reproductive risks.

Little appears to have been published on dose-response relationships or thresholds in the human population, and only preliminary data are available on quantitative extrapolation from animal tests (Chapter VI). A detailed study of these issues has recently been initiated by the Interagency Regulatory Liaison Group.

Is Scientific Knowledge of Reproductive Toxicity Sufficient to Justify Regulatory Actions?

At present, government action to regulate chemicals on the basis of their reproductive toxicity has been limited to a few cases where hazards had been demonstrated in humans at existing exposure levels (DBCP, lead, diethylstilbestrol). In most cases where evidence of reproductive toxicity is derived primarily from test systems, regulatory actions have been limited to labeling. Both types of action appear appropriate on the basis of data reviewed in this report. However, the question arises as to whether more direct action to reduce human exposure is justified in specific cases in the absence of conclusive evidence of hazards at current exposure levels. The evidence summarized in this report can be used both to support such action and to argue for caution until better methods for risk estimation are developed. The study initiated by IRLG will help to resolve this question.

Is There Scientific Justification for Differential Regulation of Exposure to Men and Women?

In recent years some chemical manufacturers and one regulatory agency have proposed regulations that would limit exposure

of female workers more stringently than that of male workers. The theory underlying such proposals is that exposure of women is more likely to lead to adverse effects than exposure of men, and specifically that it is more likely to lead to adverse effects on the fetus. Such proposals have been controversial because it is difficult to implement a differential in exposure standards without discriminating against women. Such discrimination conflicts with the goal of equal employment opportunity and would be prohibited under a proposed regulation of the Equal Employment Opportunity Commission.

The scientific basis for differential regulation is limited. Reproduction involves a wider range of processes in females than in males, and some processes in females involve critical periods of differential and development (see Chapter II). However, it does not necessarily follow that women are more sensitive to the action of any given agent. Where extensive data have been compiled on both sexes (e.g., for anesthetic gases and smelter emissions), evidence has been found for adverse effects resulting from exposure of both men and women, including some evidence for adverse fetal effects following exposure of males (See Chapter IV and Appendix A). More evidence is required to establish whether males and females differ in sensitivity. Such evidence should include not only the occurrence of effects in each sex, but also the nature of the effect and the doses at which they occur. If such evidence becomes available for a specific chemical agent, it will raise difficult issues in regulatory policy.

Concluding Comments

The present state of scientific knowledge of chemical hazards to reproduction is somewhat similar to the state of knowledge of chemical carcinogens in the late 1960s. At that time the contribution of "environmental" factors to cancer incidence in the human population was beginning to be recognized, a number of drugs and occupational exposures were known to be associated with excess cancer incidence, and many chemicals were known to be carcinogenic in experimental animals. However, the overall contribution of chemical agents to the cancer burden in the general population could not be assessed at that time, the reliability of animal experiments for prediction of human risks was in dispute, and the development of dose-response models and risk assessment procedures had scarcely begun.

The regulatory situation was also similar: only a few chemical carcinogens (other than drugs) had been regulated by federal agencies, and very few of these regulatory actions had been taken on the basis of animal data alone. The subsequent development of procedures for protecting the public against the hazards of chemical carcinogens depended on the progressive improvement of scientific knowledge of chemical carcinogenesis and of the effects of specific agents. By analogy, it can be anticipated that the acquisition of more knowledge about the effects of chemical agents on reproduction will provide the basis both for estimates of the hazards they pose and for a regulatory program.

It is not clear that chemical hazards to reproduction will prove to be as large a public health issue as chemical carcinogens or to what extent they will require regulatory attention in the 1980s. However, if reproductive hazards are an important regulatory problem, they should be predicted with as much scientific knowledge as possible. The primary purpose of this report is to draw attention to the relevant scientific issues at an early stage in their development, so that research programs can be focused on these critical issues before they become public controversies.

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APPENDIX A

COMPILATION OF HUMAN AND ANIMAL EVIDENCE
FOR ADVERSE REPRODUCTIVE EFFECTS OF
CHEMICALS AND CHEMICAL PROCESSES

EVIDENCE IN HUMANS	EVIDENCE IN ANIMALS
ALCOHOL	ALCOHOL
AMINOPTERIN	AMINOPTERIN
ANESTHETIC GASES	ANESTHETIC GASES (HALOTHANE)
BUSULFAN	ANESTHETIC GASES (NITROUS OXIDES)
CARBON DISULFIDE	ARSENIC
DDT	BUSULFAN
1,2-DIBROMO-3-CHLOROPROPANE (DBCP)	CADMIUM
DIETHYLSTILBESTROL (DES)	CARBON DISULFIDE
DIPHENYLHYDANTOIN	CARBON MONOXIDE
ETHYLENE DIBROMIDE	DDT
HEXACHLOROBENZENE (HCB)	DIBROMOCHLOROPROPANE (DBCP)
KEPONE	DIETHYLSTILBESTROL (DES)
LABORATORY REAGENTS	DIPHENYLHYDANTOIN
LEAD AND OTHER SMELTER EMISSIONS	ETHYLENE DIBROMIDE
METHOTREXATE	HEXACHLOROBENZENE (HCB)
METHYLMERCURY	KEPONE
OCCUPATIONAL EXPOSURE TO PESTICIDES	LEAD
POLYCHLORINATED BIPHENYLS (PCBs)	METHOTREXATE
THALIDOMIDE	METHYLMERCURY
TOBACCO SMOKE	NICOTINE
VINYL CHLORIDE	POLYCHLORINATED BIPHENYLS (PCBs)
WARFARIN	THALIDOMIDE
	TOBACCO SMOKE
	VINYL CHLORIDE
	WARAFIN

References cited are included in the reference list for the body of the report.

ALCOHOL--HUMAN EVIDENCE

Exposure	Dosage	Effect	Reference
"Heavy" alcohol consumption by women	Oral at least 1.6 oz (47.3 ml)/day absolute EtOH throughout pregnancy	Low birth weights, increased stillbirth rate	Kaminski et al. 1976 as reported by Streissguth et al. 1980 and U.S. Treasury/ USDHHS 1980
Alcoholism, several hundred women whose babies showed fetal alcohol syndrome	Unspecified, variable	Low birth weights, decreased infant length and head circumferences, low IQs, characteristic facial abnormalities	Streissguth et al. 1980
243 women whose babies showed fetal alcohol syndrome	About 1.4 ml absolute EtOH/kg/day throughout pregnancy	Central nervous system dysfunctions, growth deficiencies, characteristic facial abnormalities	Clarren and Smith 1978
Chronic drinking by men	Unspecified	Testicular atrophy, azoospermia; testicular pathology	Hueper 1942 and Turner et al. 1977 as reported by Hunt 1979
Drinking among 633 women given prenatal care at hospital (57 heavy drinkers and 247 moderate drinkers)	Oral; average of 174 ml absolute alcohol/day by "heavy drinkers," some alcohol more than once a month but less than 174 ml/day by "moderate drinkers," and less than one drink a month by "abstinent drinkers"	Incidence of congenital abnormalities 32% for heavy drinkers, 14% for moderate drinkers, and 9% in abstinent drinkers; malformations more severe in infants from heavy drinkers	Ouellette et al. 1977

ALCOHOL--HUMAN EVIDENCE (continued)

Exposure	Dosage	Effect	Reference
204 pregnant women clinically diagnosed as alcoholic	Unspecified	Statistically significant increased risk of spontaneous abortion, low infant birth weight (small-for-gestation-age infants in 7.8% of nonsmoking alcoholic mothers vs. 3.2% nonsmoking nonalcoholics), premature separation of placenta, precipitous delivery; increased incidence of congenital birth defects and altered development	Sokol et al. 1980 as reported by U.S. Treasury/USDHHS 1980
Moderate and social drinking by pregnant women	1-2 oz/day during pregnancy	Clinical features of abnormal growth and morphogenesis in infants	Hanson et al. 1978 as reported by U.S. Treasury/USDHHS 1980
Drinking among pregnant members of a health maintenance organization	Average of 1 oz/day before pregnancy or in late pregnancy	Statistically significant decrease in infant birth weight (91 g for exposure before pregnancy and 160 g for exposure in late pregnancy)	Little 1977 as reported by U.S. Treasury/USDHHS 1980

ALCOHOL--HUMAN EVIDENCE (continued)

Exposure	Dosage	Effect	Reference
Drinking during pregnancy	1 oz twice a week	Spontaneous abortion	Kline et al. 1980
Drinking during pregnancy	0.5-1 oz/day	Statistically significant increased risk for 2nd trimester spontaneous abortion	Harlap and Shiono 1980 as reported by U.S. Treasury/ USDHHS 1980

AMINOPTERIN--HUMAN EVIDENCE

Exposure	Dosage	Effect	Reference
Therapeutic, 12 women studied	Oral, 6-12 mg over 2-5 days during weeks 3-8 of pregnancy	Abortion in 10 of 12 cases; malformations, including hydrocephalus, meningoencephalocele, cleft plate, and hairlip, in 3 of 12 fetuses	Thiersch 1952
Therapeutic, case report for one woman	Oral, 1 mg/day for 12 days in 3rd month of pregnancy	Multiple skeletal malformations, including deformed ears and mouth, cleft palate, and immature ovaries, adrenals, and cerebellar cortex; death at 2 days	Warkany et al. 1959
Therapeutic, case report for one woman	Oral, 20 mg during several weeks in 2nd and 3rd months of pregnancy	Congenital left talipes equinovarus and multiple skull abnormalities; child still alive at 4 years	Meltzer 1956
Therapeutic, case report for one woman	Oral, 17.5 mg on 10 days during 7.5-8.5 month of pregnancy	Normal child at 2 years of age	Hill and Loeb as reported by Sokal and Lessman 1960
Therapeutic, case report for one woman	Oral, 12 mg during 1st trimester of pregnany	Anencephaly; death of infant at 12 days	Thiersch 1956

AMINOPTERIN--HUMAN EVIDENCE (continued)

Exposure	Dosage	Effect	Reference
Therapeutic, case report for one woman	Oral, undetermined quantity on days 55-58 of pregnancy	Severe malformations, including small skull, delayed ossification, marked micrognathia, and short forearms (child alive at 4.5 years)	Shaw and Steinback 1968
Therapeutic, 20 women studied	Oral, 152 mg (2 mg every 12 hours on days 34-72 of pregnancy	Abortion 18-40 days after treatment in 15 of 20 cases; multiple severe anomalies in 3 fetuses; 2 normal fetuses	Goetsch 1962
Therapeutic, case report for one woman	Oral, 29 mg over a 10-day period during weeks 6.5-8 of pregnancy	Abortion at 22-24 weeks of pregnancy; fetal malformations,including hydrocephalus, cerebral hypoplasia, talipes equinovarus, malformed ears, hypertelorism, micrognathia, and cleft palate	Emerson 1962

ANESTHETIC GASES--HUMAN EVIDENCE

Exposure	Dosage	Effect	Reference
Occupational, women working in operating rooms	Inhalation, unspecified concentration	Increased spontaneous abortions (18/31)	Vaisman 1967 as reported by NIOSH 1977c
Occupational, 745 female anesthesiologists and operating-room nurses	Inhalation, unspecified concentration	Increased spontaneous abortions after starting job (21% vs. 10%)	Askrog and Harvald 1970
Occupational, 50 female anesthesiologists	Inhalation, unspecified concentration	Increased spontaneous abortions (14/37 vs. 6/58 for control group of general physicians)	Cohen et al. 1971
Occupational; 525 female nurse anesthesists, some of whom worked during pregnancy	Inhalation, unspecified concentration	Higher incidence of birth defects for mothers working during pregnancy (71 in 434 births vs. 15 in 261); significantly higher incidence of cavernous hemangiomas, musculoskeletal and inguinal hernias, and cutaneous anomalies	Corbett et al. 1974
Occupational, 5,700 female doctors with 6,377 pregnancies occurring while mother had an anesthetic appointment	Inhalation, unspecified concentration	Decreased birth weights and increases in cardiovascular birth defects and stillbirths, but not spontaneous abortions, in working anesthetists	Pharoah et al. 1977

ANESTHETIC GASES--HUMAN EVIDENCE (continued)

Exposure	Dosage	Effect	Reference
Occupational, 1,291 male oral surgeons	Inhalation, unspecified concentration, minimum of 3 hr/wk for year before wife's pregnancy	Increased rate of spontaneous abortions in wives (16% vs. 9% in wives of 1,866 general dentists)	Cohen et al. 1975
Occupational, 67 operating-room nurses	Inhalation, unspecified concentration	Increased spontaneous abortions (10/36 vs. 3/34 in general-duty nurses)	Cohen et al. 1971
Occupational, men and women working in operating rooms	Inhalation, unspecified concentration	Increased incidence of spontaneous abortions in anesthesiologists (17% vs. 8.9% in pediatrician controls) and in operating-room nurses and technicians (19.5% vs. 15.1% in controls), but no increase in wives of anesthesiologists and of nurse anesthetists; abortion rate slightly increased in wives of operating-room nurses and technicians (18.4% vs. 10%); increased rate of birth defects in children of nurse anesthesiologists (9.6% vs. 7.6% in controls)	Cohen 1974
Occupational, 1,241 female anesthesiologists	Inhalation, unspecified concentration	Increased spontaneous abortions and birth defects with exposure in 1st and 2nd trimesters	Knill-Jones et al. 1972

ANESTHETIC GASES--HUMAN EVIDENCE (continued)

Exposure	Dosage	Effect	Reference
Occupational, 48 female anesthetists	Inhalation, unspecified concentration	Higher rate of spontaneous abortions in anesthesists (18.4% vs. 5.9% in doctors not exposed to anesthesia)	Mirakhur and Badve 1975
Occupational, 136 male anesthetists	Inhalation, unspecified concentration	Higher rate of female births (52.6%) in wives	Mirakhur and Badve 1975
Occupational, male and female anesthetists	Inhalation, unspecified concentration	Higher frequency of spontaneous abortion in exposed women but not in wives of exposed men; significantly higher frequency of major plus minor malformations (4.5% vs. 3.6% in controls), but not of only major malformations	Knill-Jones et al. 1975
Occupational, 714 women working in operating rooms (494 throughout pregnancy, 37 for more than half and 10 for less than half of pregnancy; 97 working elsewhere in hospital during pregnancy)	Inhalation, unspecified concentration	No differences from controls	Ericson et al. 1979

BUSULFAN--HUMAN EVIDENCE

Exposure	Dosage	Effect	Reference
Therapeutic, case report for one woman	Oral, 0.5-1.0 mg/day throughout pregnancy	Small but otherwise normal infant	Izumi 1956
Therapeutic, case report for one woman	Oral, 4-6 mg/day for 5 weeks during 2nd and 3rd months of pregnancy	Normal infant at birth and 1 year later	Sherman and Locke 1958
Therapeutic, case report for one woman	Oral, 4-6 mg/day from 2nd through 8th month of pregnancy	Stunting and malformations, including bilateral microphthalmia, bilateral corneal opacities, and cleft palate, in infant, who died at 10 weeks	Diamond et al. 1960
Therapeutic, case report for one woman	Oral, 2 mg every other day for first 2 trimesters and 4-10 mg/week in 3rd trimester	Normal infant	Smalley and Wall 1966

CARBON DISULFIDE--HUMAN EVIDENCE

Exposure	Dosage	Effect	Reference
Occupational, 209 women	Inhalation, <3 ppm ambient concentration	Numerous disorders of the menstrual and ovarian functions	Vasilyeva 1973 as reported by NIOSH 1977a
Occupational, 89 women	Inhalation, about 9 ppm ambient concentration	Increased incidence of spontaneous abortion (14.3% vs. 6.8%) and premature births (8.6% vs. 2.8%)	Petrov 1969 as reported by NIOSH 1977a
Occupational, 33 men	Inhalation, 13-26 ppm ambient concentration for approximately 2 years	Asthenospermia, hypospermia, teratospermia; decreased libido; impotence	Lancranjan et al. 1969 as reported by NIOSH 1977a and by Sullivan and Barlow 1979

DDT--HUMAN EVIDENCE

Exposure	Dosage	Effect	Reference
Environmental, pregnant women	Unknown	Premature infants (mean fetal blood level of DDE of 19.5 ppb in 23 premature infants vs. 5.8 ppb in 44 control full-term infants)	O'Leary et al. 1972

1,2-DIBROMO-3-CHLOROPROPANE (DBCP)--HUMAN EVIDENCE

Exposure	Dosage	Effect	Reference
Occupational, manufacture and formulation, 36 men	Inhalation, 0.3 ppm ambient concentration, more than 3 yr for some men	Azoospermia, oligospermia; severity of effects increased with length of exposure; high FSH levels in men exposed at least 3 yr	Whorton et al. 1977
Occupational, manufacture formulation, 154 men	Unknown concentrations, 1-42 months	Azoospermia, oligospermia; increased FSH levels, pathological changes in testes; severity of effects increased with exposures	Whorton et al. 1979
Occupational, 6 men aged 24-50	Unspecified, 2-10 years exposure	Azoospermia, increased plasma FSH, atrophy of the seminiferous epithelium in all 6; infertility in 2, impotence in 1	Potashnik et al. 1978
Occupational, 53 men aged 20-51, from different settings	Unspecified	Decreased sperm counts in 6 of 8 formulators and 13 of 43 users	Sandifer et al. 1979
Occupational, 18 men	Unspecified, 6-18 months	Increased frequency of Y chromosome nondisjunction (YFF) (3.8 mean% vs. 1.2 mean% in controls)	Kapp et al. 1979

DIETHYLSTILBESTROL (DES)--HUMAN EVIDENCE

Exposure	Dosage	Effect	Reference
Therapeutic, pregant women	Oral, 1.5-150 mg/day for periods of 7-252 days (total dosage in mothers of women with adenocarcinoma 135-18,200 mg) beginning during first half of pregnancy; usual therapeutic dosage 1-5 mg/day	In female offspring, increase in vaginal and cervical clear-cell adenocarcinoma, vaginal adenosis and ridges, benign abnormalities of uterus and fallopian tubes, menstrual irregularities, infrequent conception, masculinization; in male offspring, increased frequency of abnormalities in reproductive tract	IARC 1979, SRI 1978
Therapuetic, pregnant women	Oral, unspecified dose	Epididymal cysts, hypotrophic testes, capsaular induration of the testes, and sperm abnormalities in male offspring	Gill et al. 1977 as reported by Hunt 1979
Therapeutic, pregnant women	Unspecified dose	Structural changes of the uterus and fallopian tubes in female offspring	Kaufman et al. 1977
Therapeutic, pregnant women	Unspecified	Increased abortion rate, shortened gestation period, premature birth, and perinatal death	Brackbill and Berenes 1978
Occupational, women	Unknown	Hyperestrogenism; breast enlargement and pigmentation of nipples in children	Pacynski et al. 1971

DES--HUMAN EVIDENCE (continued)

Exposure	Dosage	Effect	Reference
Occupational, case report for one man	Unknown	Enlargement of breasts	Pacynski et al. 1971

DIPHENYLHYDANTOIN--HUMAN EVIDENCE

Exposure	Dosage	Effect	Reference
Therapeutic, pregnant women	Daily during months 1-4 (200-300 mg/day in 57%) of 98 pregnancies; sporadic during months 1-4 of 29 pregnancies; only after the 4th month for 78 pregnancies	Increased rates of congenital malformations, including cleft gum, lip, and palate (rates of malformed children/1,000: 61.2 for regular users during early pregnancy, 34.5 for sporadic users during early pregnancy, 51.3 for users after 4th month only)	Monson et al. 1973
Therapeutic, case reports for four pregnant women	100-400 mg daily throughout pregnancy	Malformations, including craniofacial anomalies, nail and digital hypoplasia, prenatal-onset growth deficiency, and mental deficiency	Hanson and Smith 1975
Therapeutic, case report for one woman	Oral, 100 mg daily	Three pregnancies resulting in early spontaneous abortions; one child with severe bilateral cleft lip and palate; one child with multiple malformations of the face, extremities, chest, and abdomen	Dabee et al. 1975
Therapeutic, men	Unspecified	Severe digospermia, poor sperm motility, and depressed FSH levels	Stewart-Bentley et al. 1976

ETHYLENE DIBROMIDE--HUMAN EVIDENCE

Exposure	Dosage	Effect	Reference
Occupational, men in four chemical plants in Arkansas and Texas	Inhalation, <0.5-5 ppm ambient concentration, unspecified duration	Decreased fertility in wives of workers at one plant (25.51 births expected vs. 13 observed)	Wong et al. 1979

HEXACHLOROBENZENE (HCB)--HUMAN EVIDENCE

Exposure	Dosage	Effect	Reference
Contaminated food, epidemiologic study of large-scale poisoning	50-200 mg/day for months or years; HCB detected at unspecified levels in maternal milk	Stillbirths; pink sores on skin of infants; anorexia, muscle atrophy, anemia, hyperplasia of hair follicles, death in 95% within 1 year of birth	Cam and Nigogosyan 1963, Peters 1976, Courtney 1979

KEPONE--HUMAN EVIDENCE

Exposure	Dosage	Effect	Reference
Occupational, men working at manufacturing plant	Not specified	Reproductive failure	Longford 1978
Occupational, 148 men working at manufacturing plant	Unknown	Substantial reduction in sperm motility in 13 workers	Taylor et al. 1978

LABORATORY REAGENTS--HUMAN EVIDENCE

Exposure	Dosage	Effect	Reference
Occupational, Swedish laboratory 1972-1977, 245 women	Unspecified	Increased incidence of rare malformations (29 vs. 17 expected), but no increase in prenatal death rate	Meirik et al. 1979
Occupational, Finnish chemical workers in 1973-1976, women	Unspecified	Increased incidence of spontaneous abortion (15.6 vs. 7.9 expected)	Hemminki et al. 1980
Occupational; 110 men women and 14 of their children; 22 rotoprinter workers	Unspecified; benzene and toluene	Slight increases in the frequencies of chromosome breakage (8.9-12 breaks/ 100 cells) and abnormal cells (6.3-9.9% vs. 5.5% in controls) in adults; increased frequency of chromosome breakage (11.5/ 100 cells vs. 3.0 in controls) in children)	Funes-Cravioto et al. 1977
Occupational, hospital laboratory, 56 women (71 pregnancies among 32 women)	Unspecified	Higher rate of spontaneous abortion (23% vs. 19% in women not working during pregnancy)	Strandberg et al. 1978

LEAD AND OTHER SMELTER EMISSIONS--HUMAN EVIDENCE

Exposure	Dosage	Effect	Reference
Occupational, 153 women; environmental, 1,665 women living in neighborhood of smelter	Inhalation, unspecified fied concentration	Decreased birth weights	Nordstrom et al. 1978a
Occupational, 39 men	Inhalation, unspecified concentration	Increased chromosomal gaps, chromatid aberrations	Nordenson et al. 1978a
Environmental (birth records of regional hosptial studied)	Inhalation, unspecified concentration	Decreased birth weights and increased spontaneous abortion correlated with proximity to smelter	Nordstrom et al. 1978b
Occupational and environmental, women who worked at and lived close to smelter	Inhalation, unspecified concentration	Decreased birth weights, increased birth defects and spontaneous abortions; high rate of spontaneous abortion in women whose husbands also worked at the smelter	Nordstrom et al. 1978a,b
Occupational, women	Unspecified amounts of lead	Increased abortions, stillbirths, and neonatal deaths	Oliver 1911 as reported by USEPA 1977a
Occupational, women	Lead at 75 $\mu g/m^3$	Increased abortions and stillbirths	Lane 1949 as reported by USEPA 1977a

LEAD AND OTHER SMELTER EMISSIONS--HUMAN EVIDENCE (continued)

Exposure	Dosage	Effect	Reference
Occupational, men	Unspecified amounts of lead	Increased miscarriage rate in wives	Nogaki 1958 as reported by USEPA 1977a
Environmental pollution	Unspecified amounts of lead	Increased incidence of preterm delivery and membrane rupture	Fahim et al. 1976
Occupational, men	Unspecified	Wilm's tumor in children	Kantor et al. 1979
Occupational, 150 men	Unspecified amounts of lead, 1-27 yr	Increased frequency of asthenospermia (24-51%), hypospermia(28-50%), and teratospermia (16-86%)	Lancranjan et al. 1975
Occupational, 104 women	Unspecified amounts of lead (blood lead levels of 0.110-0.317 mg%)	Increased spontaneous abortion (84.2/1,000 pregnancies vs. 45.6 before exposure to lead and 59.1 in employees not exposed to lead)	Nogaki 1957 as reported by Angle and McIntire 1964
Occupational, 8 men working in lead oxide factory	Unspecified amounts of lead	Increased secondary chromosomal aberrations, gaps, breaks, and structural alterations	Schwanitz et al. 1970

LEAD AND OTHER SMELTER EMISSIONS--HUMAN EVIDENCE (continued)

Exposure	Dosage	Effect	Reference
Occupational, men	Unspecified amounts of lead	Increased miscarriage rate in wives	Nogaki 1958 as reported by USEPA 1977a
Environmental pollution	Unspecified amounts of lead	Increased incidence of preterm delivery and membrane rupture	Fahim et al. 1976
Occupational, men	Unspecified	Wilm's tumor in children	Kantor et al. 1980
Occupational, 150 men	Unspecified amounts of lead, 1-27 yr	Increased frequency of asthenospermia (24-51%), hypospermia(28-50%), and teratospermia (16-86%)	Lancranjan et al. 1975
Occupational, 104 women	Unspecified amounts of lead (blood lead levels of 0.110-0.317 mg%)	Increased spontaneous abortion (84.2/1,000 pregnancies vs. 45.6 before exposure to lead and 59.1 in employees not exposed to lead)	Nogaki 1957 as reported by Angle and McIntire 1964
Occupational, 8 men working in lead oxide factory	Unspecified amounts of lead	Increased secondary chromosomal aberrations, gaps, breaks, and structural alterations	Schwanitz et al. 1970

LEAD AND OTHER SMELTER EMISSIONS--HUMAN EVIDENCE (continued)

Exposure	Dosage	Effect	Reference
Occupational, 26 men	Unspecified amounts of lead	Increased chromosome gaps and aberrations	Nordenson et al. 1978b
Accidental, fumes from battery burning in store, case report for one woman	Inhalation, unknown concentrations of lead, several months up to the 8th month of pregnancy (blood level of 0.24 mg%)	Normal infant, who was still normal at 4 yr 3 mo	Angle and McIntire 1964
Environmental, drinking water; case-control study of 64 retarded children and 64 matched non-retarded children	Mean lead concentration of 379 µg/liter ± standard derivation of 416)	Mental retardation significantly associated with increased lead content in drinking water and in blood	Beattie et al. 1975
Occupational, women	Unspecified amounts of cadmium	Abnormally small children (no other information provided)	Tsvetkova 1970 as reported by USEPA 1977b
Occupational, 40 men	Inhalation, various cadmium salts, atmospheric cadmium levels measured at 0.6-1.0 mg/m^3; up to 34 years	No significant differences detected in chromosomal aberrations in blood lymphocytes	O'Riordan et al. 1978

METHOTREXATE--HUMAN EVIDENCE

Exposure	Dosage	Effect	Reference
Therapeutic, case report	Oral, 5 mg/day from conception to end of 2nd month of pregnancy	Abnormalities, mostly of the skull bones	Powell and Ekert 1971
Therapeutic, case report	Oral, 2.5 mg/day for 5 days during weeks 8-10 of pregnancy	Extensive malformation of the skull, ribs, and toes, with marked growth retardation	Milunsky et al. 1968

METHYLMERCURY--HUMAN EVIDENCE

Exposure	Dosage	Effect	Reference
Environmental, contaminated fish, 23 pregnant women	Ingestion, unknown amounts	"Fetal Minamata Disease"--brain damage and cerebral palsy associated with microcephaly; disturbances in mental and motor development and in speech; defective teeth; impairment of chewing, swallowing, and gut functioning	NRC 1978
Contaminated food, case report for one woman	Ingestion, 3rd-6th, month of pregnancy	CNS damage in infant	Snyder 1971
Contaminated food, with about 1,000 persons showing signs of poisoning	Ingestion, unknown amounts	Mental retardation and cerebral palsy in infants exposed in utero	Bakir et al. 1973
Contaminated food, case report for one pregnant woman	Ingestion, unknown amounts	Tremors in infant progressing to epileptiform pattern with myoclonic jerking in infant	Curley et al. 1971 as reported by NRC 1978
Contaminated food, 29 pregnant women	Ingestion, unknown amounts (peak maternal hair concentrations of 112,000-384,000 ng/g)	Fetal brain damage apparent at 3 and 4.5 years	Marsh et al. (in press) as reported by NRC 1978

METHYLMERCURY--HUMAN EVIDENCE (continued)

Exposure	Dosage	Effect	Reference
Contaminated food, with more than 6,000 persons showing signs of poisoning	Ingestion, unknown amounts, maximum exposure during 2nd trimester and none during last 4 months of pregnancy (mercury concentration in mother's blood >200 ng/ml at time of birth and >700 ng/ml during 6th month of pregnancy)	No discernible neurological abnormalities in infant, mercury concentration in blood 2.5 times blood level in mother, sudden death at 33 days	Amin-Zaki et al. 1976
Contaminated food, 15 pregnant women	Ingestion, unknown amounts, start of exposure in 1st trimester in 4, in 2nd trimester in 4, and in 3rd trimester in 7	Gross impairment of motor and mental development, including cerebral palsy, deafness, and blindness, in 5; irritability in 6	Amin-Zaki et al. 1974
Contaminated meat, one pregnant woman	Ingestion, unknown amounts daily for 3.5 months, early pregnancy	Intermittent gross tremulous movements of the extremities in newborn, who subsequently developed myoclonic convulsions; at about 1 yr, normal physical growth, but inability to sit up or see	Pierce et al. 1972

OCCUPATIONAL EXPOSURE TO PESTICIDES

Exposure	Dosage	Effect	Reference
Occupational, sprayers and applicators	Unspecified amounts, 17 pesticides	Impotence in 4 of 5 workers	Espir et al. 1970
Occupational, 42 sprayers and applicators	Unknown amounts, herbicides and insecticides	25-fold increase in chromatid breaks and 3.5-fold increase in gaps	Yoder et al. 1973
Occupational, 25 workers in 3 insecticide plants	Unknown amounts, mostly DDT, average weekly exposure of 48 hr, 2 mo-10 yr (mean, 2 yr 4 mo)	Increased chromatid aberrations (12% vs. 8.8% in 25 workers with lower exposure and 2.2% in unexposed controls)	Rabello et al. 1975
Occupational, 5 workers	Unspecified amounts, phosphorylated insecticides	Increased chromosomal breakages, infertility	Shabati et al. 1978
Occupational, 100 workers	Unspecified amounts, chlorinated hydrocarbons, organophosphorates	Chromosome and chromatid aberrations in all workers studied who had worked with 1,2,4,5-tetrachlorobenzene	Kiraly et al. 1979
Occupational, women working in vineyards	Unspecified amounts of various pesticides (DDT, copper sulfate); DDT at 0.12 ppm in breast milk	Increased frequency of miscarriages, toxemia, uterine inertia, postpartum hemorrhage; low birth weights; histopathological changes in placentas	Nikitina 1974

POLYCHLORINATED BIPHENYLS (PCBs)--HUMAN EVIDENCE

Exposure	Dosage	Effects	Reference
Contaminated food; children and adults, including 13 pregnant women (11 with oil disease and 2 unaffected wives of men with oil disease)	For overt symptoms, minimum dose of 70-100 μg/kg/day together with 0.4 μg polychlorinated dibenzofurans/kg/day (duration in pregnant women of from last trimester to entire pregnancy)	Two stillbirths; low birth weights; dark brown stained skin in 9 infants, stained gingivae or nails in 5, increased eye discharge in 9, neonatal jaundice in 8; continuing menstrual disorders in 7 of 26 women 5 years postexposure	Kuratsune et al. 1972, 1976
Contaminated food, pregnant women with poisoning ("Yusho")	Unknown	Low birth weights, dark brown pigmentation, early eruption of teeth, gingival hyperplasia, abnormally large fontanelles, abnormally wide sagittal suture, edematous face, exophthalmos	Funatsu et al. 1971, Taki et al. 1969, Atsuko et al. 1971

THALIDOMIDE--HUMAN EVIDENCE

Exposure	Dosage	Effect	Reference
Therapeutic, analysis of more than 7,000 cases	Oral, total dose of 100 mg or more 21-36 days after conception; smallest effective dose 0.5 mg/kg/day, corresponding to blood level about 0.9 µg/ml	Phocomelia and other limb anomalies; facial hemangioma; cardiovascular anomalies; hydrocephaly; eye and ear defects; gastrointestinal and renal malformations; specific types of defect dependent on stage of gestation	Schardein 1976

TOBACCO SMOKE--HUMAN EVIDENCE

Exposure	Dosage	Effect	Reference
Cigarette smoking during pregnancy	Inhalation; less than a pack of cigarettes/day or more than a pack/day	Retarded fetal growth; increased incidence of spontaneous abortion, bleeding during pregnancy, premature and prolonged rupture of amniotic membranes, abruptio placentae, and placenta previa; fetal and neonatal deaths; increased incidence of sudden infant death syndrome; long-term lag in physical growth of children and possibly effects on their behavior and cognitive development	USDHEW 1979b, 1980

VINYL CHLORIDE--HUMAN EVIDENCE

Exposure	Dosage	Effect	Reference
Environmental and neighborhood	Inhalation, unspecified concentration	Increased incidence of birth defects, including malformations of CNS and of genital organs, cleft lip and palate, clubfoot, in residents proximal to polymerization plants	Infante et al. 1976a,b
Environmental and neighborhood (parents of 14 children with neural tube defects questioned)	Unspecified	No association of neural tube defects with residence near VC plant	Edmonds et al. 1975
Occupational, 57 men	Inhalation, unspecified concentration; average of 6-15 years of employment	Increase in chromosomal abnormalities	Purchase et al. 1978
Environmental and neighborhood of polymerization plant	Inhalation, unspecified concentration	Increased incidence of neural tube birth defects in county, but no relationship found between effect and parental employment	Edmonds et al. 1978
Occupational, 433 men	Unspecified	Increased spontaneous abortions in wives of exposed workers	Waxweiler et al. 1977

VINYL CHLORIDE--HUMAN EVIDENCE (continued)

Exposure	Dosage	Effect	Reference
Occupational, VC polymerization, 11 men	Inhalation, unspecified concentration; 4-28 of employment (average, 15 yr)	Increased incidence of chromosomal aberrations	Ducatman et al. 1975
Occupational, rubber and plastics plant; 13 polymerization workers, 4 processing workers, and 17 rubber-tire manufacturing workers	Unspecified concentrations, 10 or more years	Increased frequency of chromosomal breakage	Heath et al. 1977
Occupational, 7 workers	Unspecified concentrations, 9-29 years	Increased frequency of chromosomal aberrations (9.52% vs. 1.94% in on-site controls); highest frequency with shortest exposure	Funes-Cravioto et al. 1975
Occupational, 39 polyvinyl chloride workers	Unspecified concentrations (13 workers with known heavy exposure to VC monomer)	Statistically significant higher frequency of chromosome breakage (3.7% vs. 1.79% in controls); frequency normal 2.5 years later, after implementation of industrial hygiene controls	Hansteen et al. 1978

VINYL CHLORIDE--HUMAN EVIDENCE (continued)

Exposure	Dosage	Effect	Reference
Occupational, 45 workers	Unspecified concentration, 6-12 years	Higher frequencies of chromatid-type and unstable chromosome-type aberrations than in 44 industrial workers without exposure and in 49 controls without occupational exposure to chemicals	Szentesi et al. 1976
Occupational, 30 workers (20 with disease related to vinyl chloride exposure)	Unspecified	Higher rate of chromosome aberrations in ill workers (11.2% vs. 5.5% in controls and 7.5% in healthy workers)	Fleig et al. 1978
Occupational, manufacture of vinyl chloride monomer, 209 workers	Unspecified concentration, 1 mo-28 yr (mean, 4 yr)	No detected effects in total frequency of aberrant cells or of any particular aberration	Picciano et al. 1977

WARFARIN--HUMAN EVIDENCE

Exposure	Dosage	Effect	Reference
Therapeutic, case report for one woman	Oral, 2.5-5.0 mg/day throughout pregnancy	Nasal hypoplasia and stippled epiphyses	Shaul et al. 1975
Therapeutic, case report for one woman	Oral, 5-20 mg/day, weeks 29 and 31 of pregnancy	Death of fetus in utero	Mahairas and Weingold 1963
Therapeutic, case report for one woman	Oral, unspecified dose, 1st trimester of pregnancy	Hyperplasia of the nasal bones, stippling of the epiphyses	Pettifor and Benson 1975
Therapeutic, case report for woman	Oral, 7.5 mg/day throughout pregnancy	Premature infant; nasal hypoplasia, limb defects, eye and ear defects, bone stippling; death	Becker et al. 1975
Therapeutic, case reports for five women	Oral, total of 1,600-12,000 mg, over 15 days-31 weeks during pregnancy, beginning as early as the 8th week and as late as the 32nd week	No adverse effects detected	Mansell 1952
Therapeutic, case report one woman	Oral, total of 3,750 mg, over 73 days during last trimester of pregnancy	Fetal death due to hemorrhaging	Sachs and Labate 1949

WARFARIN--HUMAN EVIDENCE (continued)

Exposure	Dosage	Effect	Reference
Therapeutic, case reports for three woman	Oral, 5-15 mg/day from week 27-30 through pregnancy	Fetal death in all five about 5 weeks after start of therapy, but no apparent hemorrhaging	Epstein 1959
Therapeutic, case report for one woman	Oral, 7.5 mg/day throughout pregnancy	Fetal death, malformations, including marked nasal hypoplasia and abnormalities of the cartilage; no apparent hemorrhaging	Barr and Burd 1976

ALCOHOL--ANIMAL EVIDENCE

Species (and Sex)	Route	Exposure Dose and Time	Effect	Reference
Rat (F)	Intravenous	1.5 and 2 g/kg on days 6, 7, and 8 of gestation	Skeletal abnormalities of the extremities and facial areas; dose-related incidence	Sandor and Amels 1971 as reported by Fabro 1978
Rat (F)	Oral	5 ml of 40% EtOH/kg on days 8-14 of gestation	Increased resorption rate, low birth weights	Skosyreva 1973 as reported by Fabro 1978
Rat (F)	Oral, in drinking water	30% EtOH in drinking water	Reduced litter rate and size; microcephaly; dermal abnormalities and microcephaly	Tze and Lee 1975 as reported by Fabro 1978
Mouse (F)	Intraperitoneal	7.5 ml/kg at different periods during organogenesis	Increased fetal mortality rate; coloboma of the iris from treatment on days 8 and 9; absence of forepaw from treatment on day 10	Kronick 1976 as reported by Fabro 1978
Mouse (F)	Oral, in liquid diet	15-35% of calories from EtOH 30 days before and through gestation	At lower dosage, deficient occiput ossification, neural anomalies, and low birth weight; at higher dosage, cardiac and eyelid dysmorphology; dose-related prenatal death and maldevelopment	Chernoff 1977 as reported by Fabro 1978

ALCOHOL--ANIMAL EVIDENCE (continued)

Species (and Sex)	Route	Exposure Dose and Time	Effect	Reference
Mouse (M)	Unspecified	--	Mutagenic in dominant lethal test with most marked effects on epididymal spermatozoa and late spermatids	Badr and Badr 1975 as reported by Fabro 1978
Beagle dog (F)	--	3-5.3 g/kg	At high dosage, complete suppression of both intrauterine tissue differentiation and development of implanted ova; at mid-dosage, spontaneous abortion at 6-7 weeks or retention of abnormal dead fetuses; at low dosage, no effect	Ellis and Pick 1976 as reported by Fabro 1978
Guinea pig (F)	Oral	3 ml/kg; 3-4 times a week	Low birth weights, brain immaturity	Papara-Nicholson and Telford 1957 as reported by Nishimura and Tanimura 1976

AMINOPTERIN--ANIMAL EVIDENCE

Species (and sex)	Route	Exposure Dose and Time	Effect	Reference
Mouse (F)	Intraperitoneal injection	0.45 mg/kg in 3 doses on day 7 of gestation	Embryolethality; bone marrow depletion in surviving fetuses	Thiersch and Phillips 1950
Rat (F)	Injection (site unspecified)	0.2 mg/kg on days 7-13 of gestation	100% resorptions with exposure on day 9 or 10; 0-30% when exposure on the other days; 13% malformations when exposure on the 11th day; no malformations with exposure on the other days	Murphy and Karnotsky 1956
Rat (F)	Unspecified	Unspecified dose on days 4 and 5 of gestation	47% fetal resorptions; 28% litter resorptions	Thiersch 1956
Rat (F)	Unspecified	Unspecified dose on days 7 and 8 of gestation	92% fetal resorptions; 88% litter resorptions	Thiersch 1956
Rat (F)	Unspecified	Unspecified dose on days 11 and 12 of gestation	68% fetal resorptions; 44% litter resorptions	Thiersch 1956
Rat (F)	Intraperitoneal injection	Total of 0.3-0.45 mg/kg on days 5-8 of gestation (three doses at 12- to 24-hour intervals)	Embryolethality; bone marrow depletion in surviving fetuses	Thiersch and Phillips 1950

AMINOPTERIN--ANIMAL EVIDENCE (continued)

Species (and sex)	Route	Exposure Dose and Time	Effect	Reference
Rat (F)	Unspecified	0.1 mg/kg on day 6 of gestation	Defects of the eye, face, skull, brain, extremities, abdominal wall, and tail	Baranov 1966 as reported by Shepard 1980
Sheep (F)	Subcutaneous injection	1-15 mg/day on days 20-130 of gestation	Congenital malformations, including rotational and flexing deformities of the appendicular skeleton, kyphosis, scoliosis, torticollis, aplasia of the mandible	James and Keeler 1968
Macaque monkey (F)	Unspecified	1.0 mg/kg on days 38-39 of pregnancy	No adverse effects	Delahunt 1966 as reported by Wilson 1971
Macaque monkey (F)	Unspecified	0.1-0.2 mg/kg on days 21-33 and 26-28 of pregnancy	Abortion in two of two monkeys	Delahunt 1966 as reported by Wilson 1971

ANESTHETIC GASES (HALOTHANE)--ANIMAL EVIDENCE

Species (and Sex)	Route	Exposure Dose and Time	Effect	Reference
Rat (F)	Inhalation	0.8% on days 6-10 of gestation	Lumbar ribs and separation of fused lateral ossification centers; peak effect on day 8 or 9.5	Basford and Fink 1968
Rat (F)	Inhalation	12,500 ppm on day 3 or 10 of gestation	In adult offspring, hyperalgesia and 40% more errors in learning a visual discrimination to escape footshock	Bowman and Smith 1977
Rat (F)	Inhalation	10 ppm, 8 hr/day for entire gestation	Focal cytoplasmic degradation and necrosis in liver tissues	Chang et al. 1975
Rat (M and F)	Inhalation	1.34-1.48%, 1 hr/day, 1-11 times, 5-15 days before mating	No adverse effect on mating or fertility	Kennedy et al. 1976
Rat (F)	Inhalation	1.35-1.43%, days 1-5, 6-10, and 11-15 of gestation	Rates of implatations, resorptions, viable fetuses, and skeletal defects similar to rates in controls	Kennedy et al. 1976
Rabbit (F)	Inhalation	2.16-2.30%, days 6-9, 10-14, and 15-18 of gestation	Rates of implatations, resorptions, viable fetuses, and skeletal defects similar to rates in controls	Kennedy et al. 1976

ANESTHETIC GASES (HALOTHANE)--ANIMAL EVIDENCE (continued)

Species (and Sex)	Route	Exposure Dose and Time	Effect	Reference
Rat (F)	Inhalation	1.44%, 1 hr/day on days 15-20 of gestation	Small litters; fetal survival and body weights normal; no malformations reported	Kennedy et al. 1976
Rat (F)	Inhalation	50-3,200 ppm 8 hr/day on days 8-12 of pregnancy	No apparent effects on fetal growth, survival, and skeletal development	Lansdown et al. 1976
Rat (F)	Inhalation	1,600 ppm 8 hr/day, day 1-21 of gestation	Retarded fetal growth but no effects on skeletal system	Lansdown et al. 1976
Mouse (F)	Inhalation	10,000 or 15,000 ppm, 3 hr/day on days 12-15 of gestation	Increased incidence of cleft palate and limb developmental defects	Smith et al. 1971

ANESTHETIC GASES (NITROUS OXIDES)--ANIMAL EVIDENCE

Species (and Sex)	Route	Exposure Dose and Time	Effect	Reference
Hamster (F)	Inhalation	60% N_2O and 0.6% halothane days 9-11 of gestation	Increased resorptions; decreased fetal weight; decrease in crown-rump length	Bussard et al. 1974
Rat (F)	Inhalation	45-50% on days 8-14 of gestation	Abnormalities of ribs and vertebrae; death and resorption of fetuses	Fink et al. 1967
Rat (F)	Inhalation	Single exposure at 700,000 ppm between days 5 and 11 of gestation	Fetal skeletal anomalies; peak effect on day 9	Shepard and Fink 1968
Rat (F)	Inhalation	100, 1,000, or 15,000 ppm, 8 or 24 hr/day for entire gestation	Fetal death (rates higher at 1,000 and 15,000 ppm)	Corbett et al. 1973
Rat (M)	Inhalation	200,000 ppm, 8 or 24 hr/day for 0-35 days after birth	Reversible effects on spermatogenesis	Kripke et al. 1976

ARSENIC--ANIMAL EVIDENCE

Species (and Sex)	Route	Exposure Dose and Time	Effect	Reference
Rat (F)	Intra-peritoneal	20-40 mg/kg once during days 7-12 of gestation	Subcutaneous hemorrhages of all fetuses, soft-tissue malformations of the eye (anophthalmia and microphthalmia), exencephaly, renal agenesis, gonadal agenesis, rib defects, vertebral ossification	Beaudoin 1974
Mouse (F)	Intra-peritoneal	45 mg sodium arsenate/kg on days 6-12 of gestation	Increased fetal absorption; decreased fetal weight; extensive malformations, including exencephaly, micrognathia, protruding tongue, agnathia, open eye exophthalmos, anophthalmia, missing pina, cleft lip, hydrocephalus, unbilical hernia, eventration, ectrodactyly, micromelia, and shortened or twisted tail and twisted limb or both; skeletal defects, such as fused vertebrae and fused or forked ribs	Hood and Bishop 1972

ARSENIC--ANIMAL EVIDENCE (continued)

Species (and Sex)	Route	Exposure Dose and Time	Effect	Reference
Hamster (F)	Intravenous	15-25 mg/kg on day 8 of gestation	Malformations of the cranium and ribs, renal agenesis, other genito-urinary abnormalities, cleft lip and palate, and anophthalmia	Ferm et al. 1971
Hamsters (F)	Intravenous	Sodium arsenic at 20 mg/kg on day 8 of gestation	High incidence of exencephaly	Ferm and Carpenter 1968
Hamster (F)	Injection in lingual vein	20 mg/kg on day 8 of gestation	49% malformations, including encephalocele exencephaly, cleft palate and lip, ear malformations; 84% malformed resorbed embryos	Holmberg and Ferm 1969

BUSULFAN--ANIMAL EVIDENCE

Species (and Sex)	Route	Exposure Dose and Time	Effect	Reference
Rat (F)	Unspecified	10 mg/kg on days 14-16 of gestation	Absence of germinal cells and sterility in male and female offspring	Bollag 1954 as reported by Sokal and Lessman 1960
Rat (F)	Unspecified	Unspecified dose on days 4 and 5 of gestation (two doses of an amount that, if given on 5 subsequent days, would have caused death in half of the animals)	51% fetal resorptions; 25% litter resorptions	Thiersch 1956
Rat (F)	Unspecified	Unspecified dose on days 7 and 8 of gestation	8% fetal resoprtions	Thiersch 1956
Rat (F)	Unspecified	Unspecified dose on days 11 and 12 of gestation	7% fetal resorptions	Thiersch 1956

BUSULFAN--ANIMAL EVIDENCE (continued)

Species (and Sex)	Route	Exposure Dose and Time	Effect	Reference
Rat (F)	Intraperitoneal injection	34 mg/kg on day 12 of gestation	Decreased weight and length; syndactylous rear- and forepaws; short, kinky tails; skeletal malformations of the rib, sternum, and scapula	Murphy et al. 1958
Rat (F)	Intraperitoneal injection	10 mg/kg on days 13-15 of gestation	Ovarian dysgenesis in fetuses; small litters and low birth weights	Heller and Jones 1964
Rat (F)	Intraperitoneal injection	10 mg/kg on day 13 of gestation	Destruction of the seminiferous tubules in surviving fetuses	Vanhems and Bousquet 1972

CADMIUM--ANIMAL EVIDENCE

Species (and Sex)	Route	Exposure Dose and Time	Effect	Reference
Rat (F)	In utero injection into fetuses	Unspecified dose on days 18 and 19 of gestation	14% fetal mortality	Levin and Miller 1978
Rat (F)	Oral; in drinking water	1.6 on days 9-11 of gestation	Fetal mortality; decreased weight; hydrocephaly; cryptochidum; hydronephrosis; anophthalmia or microphthalmia	Barr 1973
Rat (F)	Subcutaneous	4-12 mg/kg on days 14-17 of gestation	Fetal deaths, decreased fetal weight, and malformations, including agnatha, cleft palate, and hypopiastic lungs in fetuses	Chernoff 1973
Rat (F)	Subcutaneous	Unspecified dose on days 12-15 of gestation	Fetal mortality and growth retardation; lung hypoplasia; effects on lung surfactant; respiratory distress in some pups	Daston and Grabowski 1979
Rat (F)	Intravenous	1.25 mg Cd^{+2}/kg once between days 9 and 12 of gestation	80% hydrocephalus	Samarawickrama and Webb 1979

CADMIUM--ANIMAL EVIDENCE (continued)

Species (and Sex)	Route	Exposure Dose and Time	Effect	Reference
Mouse (M)	Intraperitoneal	1.0 mg/kg; unspecified time	Partially reversible decrease in male fertility; no evidence of gross microscopic morphological changes in the testis	Lee and Dixon 1973
Mouse (F)	Unspecified	Unspecified dose on day 7 of gestation	Decreased weight, exencephalia, excessive nucleic acid synthesis, and decreased growth of the brain	Keino and Goto 1975
Mouse (F)	Subcutaneous	10 mg/kg once between days 14 and 17 of gestation	Death of embryo; uterine hemorrhaging; alterations of the vascular system	Chiquoine 1965
Mouse (F)	Subcutaneous	10 mg/kg on day 1, 2, 3, 4, or 5 of gestation	Fertility decreased; lowest fertility in mice exposed on day 5 (1/5 vs. 2/3, 3/3, 2/3, and 3/3 on days 1, 2, 3, and 4, respectively)	Chiquoine 1965

CADMIUM--ANIMAL EVIDENCE (continued)

Species (and Sex)	Route	Exposure Dose and Time	Effect	Reference
Mouse (F)	Intraperitoneal	12-24 μmoles/kg on day 9 of gestation	Malformations of the limbs, face, trunk, and tail	Layton and Layton 1979
Mouse (F)	Oral; in drinking water	10, 20, or 40 ppm throughout gestation	Various degrees of fetal growth retardation; severe anemia in newborns	Webster 1978
Hamster (F)	Intravenous	2 mg/kg on day 8 of gestation	Resorption of fetuses; cleft palate and deformities in the primative neural tubes; exencephalia; microphthalima; gross malformations of fore and hind limbs, including amelia, micromelia, and ectodactyly	Gale and Ferm 1973

CARBON DISULFIDE--ANIMAL EVIDENCE

Species (and Sex)	Route	Exposure Dose and Time	Effect	Reference
Rat (F)	Inhalation	13.3 mg/m^3, 4 hr/day for entire gestation (21 days)	Fetal malformations, decreased organ-to-body weight ratios and nervous system dysfunctions in offspring	Sal'nikova and Chirkova 1974
Rat (M)	Inhalation	2.2-13.3 mg/m^3, 4 hr/day for entire gestation (21 days)	No effect	Sal'nikova and Chirkova 1974
Rat (F)	Inhalation	50-200 mg/m^3 for entire pregnancy	Increased level of free fatty acids in liver of mothers; decreased levels of triglycerides and phospholipids in mothers and in fetuses	Balabaeva and Tabocova 1979
Rat (F)	Inhalation	50, 100, or 200 mg/m^3 for entire gestation (21 days)	Impairment of prenatal development with increase of early embryonal lethality, reduction in fetal weight, and a high incidence of malformations of the brain and limbs	Tabocova et al. 1978
Rat (M)	Inhalation	Unspecified	Alterations in spermatogenesis	Artamonova and Klishova 1972

CARBON DISULFIDE--ANIMAL EVIDENCE (continued)

Species (and Sex)	Route	Exposure Dose and Time	Effect	Reference
Rat (F), mouse (F)	Inhalation	2,000 mg/m^3 for 2 hr/day for entire pregnancy	Increased fetal mortality, decreased fertility	Yaroslavskiy 1969 as reported by NIOSH 1977a
Rat (M)	Intraperitoneal	78 mg/kg every other day for 4 months	Testicular lesions; no spermatogenesis	Gondzik 1971 as reported by NIOSH 1977a
Rat (M)	Intraperitoneal	78 mg/kg every other day for 2 months	Decreased number of spermatozoa; blood vessels engorged, walls thickened	Gondzik 1971 as reported by NIOSH 1977a
Rat (F)	Inhalation	12 mg/m^3 for 70-110 days before mating and during pregnancy	Increased fetal mortality, terata	Barilyak et al. 1975 as reported by NIOSH 1977a

CARBON MONOXIDE--ANIMAL EVIDENCE

Species (and Sex)	Route	Exposure Dose and Time	Effect	Reference
Rat (F)	Inhalation	Concentration of 150 ppm throughout gestation	Increased amplitude of components of visual evoked potentials, which may indicate altered central nervous system function, in 65-day old offspring	Dyer et al. as reported by USDHEW 1980
Rat (F)	Inhalation	Concentration of 15,000 ppm (1.5%) or 5,900 ppm for 5-8 min 10 times on alternate days during gestation	Abortion or absorption of most fetuses with 15,000 ppm; fewer rats affected with lower dose	Wells 1933 as reported by USDHEW 1979b
Rat (F)	Inhalation	Concentration of 3,400 ppm (0.34%) for 1 hour daily for 3 mo or for 150 days	Fewer pregnancies, small litters, low neonatal survival; no pregnancies in rats exposed for 150 days	Williams and Smith 1935 as reported by USDHEW 1979b
Rat (F)	Inhalation	Concentration of 150 ppm throughout gestation	Low birth weight, low neonatal weight gain, low spontaneous and L-dopa-stimulated activity in young	Fechster and Annau 1977 as reported by USDHEW 1980

CARBON MONOXIDE--ANIMAL EVIDENCE (continued)

Species (and Sex)	Route	Exposure Dose and Time	Effect	Reference
Rat (F)	Inhalation	Concentration of 30 or 90 ppm throughout gestation	No effect on fetal total body weight; high fetal brain and lung weights with 90 ppm	Garvey and Longo 1978 as reported by USDHEW 1979b
Mice (F), Rabbits (F)	Inhalation	Concentration of 250 ppm for 7 or 24 hours/day, on days 6-15 of gestation in mice and 6-18 in rabbits	Fetal mouse weight slightly increased with 7-hour exposure and slightly decreased with 24-hour exposure; increased minor skeletal variants, such as extra lumbar ribs and spurs	Schwetz et al. 1979 as reported by USDHEW 1980
Rabbit (F)	Inhalation	Concentration of 90 or 180 ppm continuously for 30 days	Low birth weights and high neonatal death rate; limb deformities in newborns with 180 ppm	Astrap et al. 1972 as reported by USHDEW 1979b

DDT--ANIMAL EVIDENCE

Species (and Sex)	Route	Exposure Dose and Time	Effect	Reference
Rat	Oral; in diet	p,p'-DDT at dietary concentration of 20, 200, or 500 ppm for 6 mo	At 500 ppm, death of all offspring within 10 days of birth; at 200 ppm, severe depression of growth in offspring; at 20 ppm, no effects	Clement and Okey 1974
Rat	Oral; in diet	o,p'-DDT at dietary concentration of 20, 200, or 1,000 ppm for 6 mo	At 1,000 ppm, reduced fertility and, in offspring, reduced fecundity; at 20 and 200 ppm, no effects on reproductive performance of offspring	Clement and Okey 1974
Rat	Oral; in diet	Technical DDT at dietary concentration of 10, 100, and 600 ppm for 2 yr or 50 ppm for 2 generations	No survival of offspring in 2nd generation with 600 ppm; reduction in preweaning survival with 50, 100, and 600 ppm; no effects on reproduction with 10 ppm	Fitzhugh and Nelson 1947, Fitzhugh 1948
Rat	Oral; in diet	Technical DDT at dietary concentration of 20 or 200 ppm for 2 generations	Increase in incidence of ring-tail; normal reproduction at 200 ppm; increased reproductive life span relative to controls at 20 ppm	Ottoboni 1969
Rat	Oral; in diet	Dietary concentration of 75 and 150 ppm for 8-36 week	Reproductive failure at 150 ppm; reduction in number of females producing litters at 75 ppm	Jonsson et al. 1975

DDT--ANIMAL EVIDENCE (continued)

Species (and Sex)	Route	Exposure Dose and Time	Effect	Reference
Rat	Oral; in diet	Dietary concentration of 1 ppm for 175 days or 15 ppm for 2 generations	No effects	Duby et al. 1971
Rat	Oral; in diet	Dietary concentration of 7 ppm for 2 generations	Marked reduction in fertility and in survival of offspring from 1st generation; no conceptions in rats in 2nd generation	Green 1969
Rat	Oral; in diet	Dietary concentration of 2.5, 12.5, or 25 ppm for 3 generations	Slight increase in mortality of offspring	Treon and Cleveland 1955
Rat	Oral; in diet	o,p'-DDT at dietary concentration of 1 or 2.5 ppm for 168 days or through pregnancy and lactation	No significant effects	Wrenn et al. 1970
Rat	Oral; in diet	Technical DDT at dietary concentration of 250 ppm for 2 generations	Increased preweaning mortality of offspring	Tomatis et al. 1972
Mouse	Oral; in diet	Dietary concentration of 25, 100, or 250 ppm for 6 generations	At 250 ppm, severe adverse effects on reproduction, primarily on lactation and survival of offspring; at 100 ppm, slight reduction in lactation and survival of offspring; at 25 ppm, no effects	Keplinger et al. 1968

Species (and Sex)	Route	Exposure Dose and Time	Effect	Reference
Mouse	Oral; in diet	Technical DDT at dietary concentration of 250 ppm for 4 generations	No effect	Terracini et al. 1973a,b
Mouse	Oral; in diet	Technical DDT at 25 or 50 mg/kg/day for 10 days	Reduction in accumulation of testosterone and 5-alpha-dihydrotestosterone by anterior prostate	Lloyd et al. 1974
Mouse	Oral; in diet	Technical DDT at 2.5 mg/kg once during pregnancy	Delayed acquisition of conditioned avoidance responses by offspring at age 32-37 days	Al-Hachim and Fink 1967, 1968
Mouse	Oral; in diet	Technical DDT at dietary concentration of 7 ppm for 120 days	No effects	Ware and Good 1967
Mouse	Oral; in drinking water	Concentration of 0.01, 0.1, or 1.0 ppb for 8 wk during and after pregnancy	At 0.1 and 1.0 ppb, significant decrease in aggressive behavior of male offspring at age 35 days; at 0.01 ppb, no effects on agressive behavior of male offspring	Scudder and Richardson 1970
Mouse	Oral	p,p'-DDT at 1 mg/kg on days 10, 12, and 17 of gestation	Morphologic changes in gonads and reduction in fertility of offspring, especially in females; no gross teratogenic effects	McLachlan and Dixon 1972

DDT--ANIMAL EVIDENCE (continued)

Species (and Sex)	Route	Exposure Dose and Time	Effect	Reference
Rabbit	Oral	p,p'-DDT at 50 mg/kg on days, 7, 8, and 9 of gestation	Premature delivery, increase in resorptions, decreased intrauterine growth, no congenital abnormalities	Hart et al. 1971
Dog	Oral; in diet	p,p'-DDT at 12 mg/kg/day for 14 mo	Diminished libido in males, delayed estrus in females, reduction in mammary development and milk production, infertility, increased infant and maternal mortality	Deichmann et al. 1971, Deichmann and MacDonald 1971
Dog	Oral; in diet	Technical DDT at 1, 5, or 10 mg/kg/day for 3 generations	Earlier onset of estrus in exposed females than in controls, but reproduction otherwise normal	Ottoboni et al. 1977

DIBROMOCHLOROPROPANE (DBCP)--ANIMAL EVIDENCE

Species (and Sex)	Route	Exposure Dose and Time	Effect	Reference
Rat (M), guinea pig (M), rabbit (M)	Inhalation	12 ppm/7 hr/day 70-92 days	Severe atrophy and degeneration of the testes	Torkelson et al. 1961
Rat (F)	Gavage	12.5-50 mg/kg on days 6-15 of gestation	Low-birth-weight offspring at higher dosages from dams showing reduced maternal weight gain	Ruddick and Newsome 1979
Rat (M)	Oral	0.5-5.0 mg/kg "for long periods of time"	Inhibition of gonadotropic function on the testicles	Faidysh and Aukhimenko 1974
Rats (M and F)	Oral	10-100 mg/kg	Gonadotoxic effect; disturbances of hormonal functions, spermatogenesis, and estrous cycle	Reznik and Sprinchan 1975

DIETHYLSTILBESTROL (DES)--ANIMAL EVIDENCE

Species (and Sex)	Route	Exposure Dose and Time	Effect	Reference
Mouse (F)	Subcutaneous	0.01-100 µg/kg on days 9-16 of gestation	In female offspring, dose-dependent decrease in fertility, with complete sterility at 10 and 100 µg/kg; abnormalities of genital tract, including cystic hyperplasia of the endometrium and uterine adenocarcinoma; in male offspring, sterility in 60% at 100 µg/kg, with alterations in reproductive tract, including metaplastic and neoplastic tissue	McLachlan as reported by Bingham 1976
Mouse (F)	Subcutaneous	DES disodium salt at at 10 mg/kg on day 7, 9, 11, 13, 15, 17, or 19 of gestation	In female offspring, urogenital abnormalities with exposure on days 15, 16, or 17, increased incidence of ovarian tumors; in male offspring, inhibition of growth and undescended testes with exposure on days 17 and 19; in both sexes, increased incidence of lung tumors	Nomura and Kanzaki 1977 as reported by IARC 1979

DES--ANIMAL EVIDENCE (continued)

Species (and Sex)	Route	Exposure Dose and Time	Effect	Reference
Rat (F)	Subcutaneous	10-42 mg from day 12 or 13 to day 18-21 of gestation	Reduced litter size; feminization of genitalia of male offspring	Greene et al. 1940 as reported by IARC 1979
Rat (F)	Subcutaneous	0.015-0.6 mg/kg on days 13, 16, 18, and 20 of gestation	Urogenital abnormalities in male and female offspring; inhibition of growth and descent of testes	Vorherr et al. 1979 as reported by IARC 1979
Rat (F)	Oral	100 µg/kg on day 15 of gestation	Lowered hepatic histidase activity in adult female offspring	Lamartiniere and Lucier 1978
Hamsters (F)	Oral; gastric intubation	20 or 40 mg/kg on day 15 of gestation or 20 or 40 mg/kg on days 14 and 15	High incidences of metaplastic, dysplastic, and neoplastic lesions of various segments of the genital tract in male and female offspring	Rustia 1979, Rustia and Shubik 1976 as reported by IARC 1979
Rabbit (F)	Injection; unspecified site	0.5-5.0 mg before days 12-14 of gestation	Abortion	Adams et al. 1961 as reported by IARC 1979
Rhesus monkeys (F)	Oral	1 mg/day from day 21, 100, or 130 of gestation to delivery	Vaginal ridging, cervical hooding, and some vaginal adenosis in female offspring	Henricks et al. 1979 as reported by IARC 1979

DIPHENYLHYDANTOIN--ANIMAL EVIDENCE

Species (and Sex)	Route	Exposure Dose and Time	Effect	Reference
Mice (F)	Oral intubation	150 mg/kg on days 11, 12, and 13 of gestation	Cleft palate	Lorne and Fraser 1973
Mice (F)	Intraperitoneal (ip), subcutaneous, or oral (intubation)	50, 75, 100, or 150 mg/kg once, on one of days 8-15 of gestation	Increased resorption rate (80% resorption with 150 mg/kg ip on day 10 or 14); reduced fetal weight with exposure on days 9-15; day- and dose-dependent shortening of fetal long bones; various anomalies, including open eye, ectrodactyly, cleft lip, cleft palate, hydronephrosis, and internal hydrocephalus (none with 50 mg/kg); skeletal defects	Harbison and Becker 1969
Mice (F)	Intraperitoneal (ip), subcutaneous, or oral (intubation)	50, 75, or 87.5 mg/kg on days 8-10 or 12-14 of gestation	Increased resorption rate with 87.5 mg/kg ip; shortening of fetal long bones; cleft palate and syndactyly; dose-related lack of fusion of sternebrae with exposure on days 12-14	Harbison and Becker 1969

DIPHENYLHYDANTOIN--ANIMAL EVIDENCE (continued)

Species (and Sex)	Route	Exposure Dose and Time	Effect	Reference
Monkey (F)	Oral	5-50 mg/kg/day at various intervals during days 19-45 of gestation	Minor urinary tract anomaly at 5-20 mg/kg; possibly a slight increase in abortions at 20-50 mg/kg	Wilson 1973

ETHYLENE DIBROMIDE--ANIMAL EVIDENCE

Species (and Sex)	Route	Exposure Dose and Time	Effect	Reference
Rat (M)	Intra-peritoneal	5 doses at 10 mg/kg/day	Selectively damaged spermatids; transient sterility as measured by average size of litters from several mated female rats	Edwards et al. 1970
Rat (F)	Inhalation	32 ppm, 23 hr/day on days 6-15 of gestation	Decreased implants/dam, fetuses/dam, and fetal weight; malformations, including wavy ribs and hydrocephaly	Short et al. 1976
Rat (M)	Inhalation	19, 39, or 89 ppm, 7 hr/day for 10 wk	At the high dose, reduced testicular weights and serum testosterone levels; unsuccessful mating over a 2-week period; no effects with exposure at 19 and 39 ppm	Short et al. 1979
Rat (F)	Inhalation	10, 39, or 80 ppm, 7 hr/day for 3 wk	Mortality and morbidity in high-dose group; although cycles abnormal until after exposures, no effect on reproduction; normal litters	Short et al. 1979
Rat (F), mouse (F)	Inhalation	20, 38, or 80 ppm, 23 hr/day on days 6-16 of gestation	Decreased weight gain, food consumption, and survival	Short et al. 1978

ETHYLENE DIBROMIDE--ANIMAL EVIDENCE (continued)

Species (and Sex)	Route	Exposure Dose and Time	Effect	Reference
Mouse (F)	Inhalation	32 ppm, 23 hr/day on days 6-15 of gestation	Low weights in live fetuses; increased skeletal abnormalities, including lack of ossification of the incus bone, variations in the supraoccipital bone and sternabrae, and hydrocephaly	Short et al. 1976
Sheep (F)	Oral fumigated "concentrate"	3,000 ppm	No apparent detrimental effect on reproductive ability	Bondi and Alumot 1967
Sheep (M)	Subcutaneous injection	7.8-13.5 mg/kg day for 12 days	Transient teratospermia; decreased motility; structural abnormalities in the acrosome, nucleus, and mitocondrial sheath	Eljack and Hrudka 1979
Bull (M)	Oral capsule	4 mg/kg/day on alternate days for a total of 10 doses	High percentage of sperm abnormalities; decreased sperm motility	Amir and Ben-David 1973
Bull (M)	Oral capsule	4 mg/kg/day on alternate days for 12-21 days	Abnormal spermatazoa in testes, epididymis, ductus deferens, and ejaculate	Amir 1973
Cows (F)	Oral capsule	1 or 2 mg/kg/day from 2nd-3rd mo of pregnancy to 3rd lactation periods	Possible effect on fertility although gestation and parturition appeared normal	Bondi and Alumot 1967

HEXACHLOROBENZENE (HCB)--ANIMAL EVIDENCE

Species (and sex)	Route	Exposure Dose and Time	Effect	Reference
Rat (M and F)	Oral; in diet	Dietary concentration of 10-640 ppm before mating and throughout gestation	Decreased litter size and stillbirths at 160 and 320 ppm; reduced postnatal survival at 80-160 ppm; reduced birth weight at 80 ppm; no effects at 40 ppm	Somers et al. 1970 and Grant et al. 1974 as reported by Courtney 1979
Monkey (F)	Oral	8-128 mg/kg, 60 days	Histopathological changes in ovaries, which were slight at 8 or 32 mg/kg and extensive at the highest dose levels	Itropoulos et al. 1976 as reported by Courtney 1979

KEPONE--ANIMAL EVIDENCE

Species (and Sex)	Route	Exposure Dose and Time	Effect	Reference
Sheepshead minnow	In water	Concentration of 0.08-24 µg/liter for 28 days before spawning	Embryotoxicity; malformations; decreased length and some scoliosis in juvenile fish	Hansen et al. 1977
Japanese quail (M)	Oral	Dietary concentration of 200 ppm, 0-42 days	Structural deterioration of testes; enlargement and atrophy; apparently depressed spermatogenesis	Eroschenko 1978
Rat (F)	Gastric intubation	2-10 mg/kg on days 7-16 of gestation	Fetal toxicity, reduced fetal weight, reduced ossification, edema, undescended testis, enlarged renal pelvis, enlarged cerebral ventricles	Chernoff and Rogers 1976
Rat (F)	Gastric intubation	2-4 mg/kg/day on days 2-21 of gestation	Fetotoxicity; stillbirths and abortions; strong evidence of CNS impairment in the perinatal rats	Rosenstein et al. 1977
Rat (F)	Gavage	15 mg/kg/day on days 14-20 of pregnancy	Persistent vaginal estrus, anovulation, and toxic levels of serum estradiol in female offspring	Gellert and Wilson 1979

KEPONE--ANIMAL EVIDENCE (continued)

Species (and Sex)	Route	Exposure Dose and Time	Effect	Reference
Rat (M and F)	Oral	Dietary concentration of 25 ppm for 3 months before mating	Reproduction in females completely inhibited (partially restored in 2 months); hyperplasia of adrenal cortex; no effect in males	Cannon and Kimbrough 1979
Rat (M and F)	Oral	Dietary concentration of 30 ppm for 7 weeks before mating	Smaller litters sired by treated males; females in constant estrus; low estradiol; decreased luteinizing hormone levels; increased uterine weights; decreased ovarian weights	Hammond et al. 1978
Mouse (F)	Gastric intubation	2-12 mg/kg on days 7-16 of gestation	Increased fetal mortality and clubfoot	Chernoff and Rogers 1976
Mouse (F)	Oral	Dietary concentration of 10 ppm for 1 month before mating	Decrease in size and numbers of litters	Good et al. 1965
Mouse (F)	Oral	30 ppm	Constant estrus; reduced luteinizing hormone, which prevented normal ovulation	Haber 1965

LEAD--ANIMAL EVIDENCE

Species (and Sex)	Route	Exposure Dose and Time	Effect	Reference
Rat (M)	Oral; in diet	Lead nitrate at several levels for 30 days before mating	Infertility in males	Puhac et al. 1963 as reported by Singhal and Thomas 1980
Rat (M)	Unspecified	Lead acetate at 5 and 100 µg/day	Decreased sperm motility; prostatic hyperplasia	Hilderbrand et al. 1973 as reported by Singhal and Thomas 1980
Rat (M)	Parenteral	Unspecified	Germinal epithelium damage in males	Timm and Schulz 1966 as reported Singhal and Thomas 1980
Rat (M and F)	Oral; in diet	Lead acetate at 1% in diet from before mating through lactation	Reductions in litter size, birth weights, and survival; additive effects when males and females were treated together	Stowe and Goyer 1971 as reported by USEPA 1977a
Rat (M and F)	Oral; in diet	Lead at 512 ppm in diet before mating	Reduction in weaning percentage	Morris et al. 1938 as reported by USEPA 1977a

LEAD--ANIMAL EVIDENCE (continued)

Species (and Sex)	Route	Exposure Dose and Time	Effect	Reference
Rat (F)	Oral; in drinking water	Lead acetate at 0.5-250 ppm from weaning through reproduction and lactation	Low birth weight and delayed physical development in offspring from higher dose levels	Kimmel et al. 1976 as reported by USEPA 1977a
Rat (F)	Oral; in drinking water	25 ppm during entire pregnacy	Death before weaning, runting	Schroeder and Mitchener 1971
Rat (F)	Intravenous	Lead nitrate at 35-70 mg/kg once during days 8-15 of gestation	External malformations; urorectal malformations; axial skeletal defects with exposure on days 8 and 9; marked increase in resorption rate with exposure on days 10-15	McClain and Becker 1975 as reported by Singhal and Thomas 1980
Mouse (M)	Oral; in drinking water	2% aqueous solution of lead subacetate	Infertility in males	Verma et al. 1974 as reported by USEPA 1977a
Mouse (M)	Oral; in diet	Lead acetate at 1% in diet	Increase in number of abnormal sperm by 8 weeks	Eyden et al. 1978 as reported by Singhal and Thomas 1980

LEAD--ANIMAL EVIDENCE (continued)

Species (and Sex)	Route	Exposure Dose and Time	Effect	Reference
Mouse (F)	Intravenous	Lead nitrate at 50 mg/kg on days 10 or 12 of gestation	With exposure on day 12, cleft palate in 33% of fetuses; with exposure on day 10, nonossification of cervical ventri in 27% of fetuses	McClain and Becker 1970 as reported by Singhal and Thomas 1980
Mouse (F)	Unspecified	Lead chloride at 100 mg/kg on day 9 of gestation	Incomplete or delayed ossification; low birth weights (lead chloride)	McLellan et al. 1974 as reported by Singhal and Thomas 1980
Mouse (F)	Oral; in diet	0.125-0.5% in diet on days 1-16 of gestation	Reduction in number of pregnancies at higher dose levels	Jacquet et al. 1975 as reported by Singhal and Thomas 1980
Mouse (F)	Oral; in drinking water	25 ppm during entire pregnancy	Failure to reproduce three generations, runting, death before weaning	Schroeder and Mitchener 1971
Golden hamster (F)	Intravenous	Various lead salts at 50 mg/kg on day 8 of gestation	Embryonic mortality and severe malformations of sacral-tail region	Carpenter and Ferm 1977

LEAD--ANIMAL EVIDENCE (continued)

Species (and Sex)	Route	Exposure Dose and Time	Effect	Reference
Rhesus monkey (F)	Unspecified	Unspecified	Histopathological changes in ovaries	Vermande-van Eck and Meigs 1960 as reported by USEPA 1977a

METHOTREXATE--ANIMAL EVIDENCE

Species (and Sex)	Route	Exposure Dose and Time	Effect	Reference
Rat (F)	Intraperitoneal injection	0.2 mg/kg on day 9 of gestation	64% resorptions; 30% malformations	Wilson 1971
Mouse (F)	Intraperitoneal injection	One dose of 0.3-50 mg/kg on day 10 of gestation	Increased resorptions and malformations; with doses of 10 mg/kg and higher, ectrodactyly and cleft palate	Skalko and Gold 1974
Rabbit (F)	Intravenous injection	9.6 mg/kg on day 10 of gestation	50% fetal mortality; 25% malformations in survivors	Jordan et al. 1970
Cat (F)	Oral, gelatin capsules	0.5 mg/kg/day on days 11-14, 14-17, or 17-20 of gestation	Maternal toxicity and increased incidence of abortion; with dosing on days 14-17 or 17-20, highest percentage of malformations, including umbilical hernia, retarded ossification of calvarium, and other anomalies	Khera 1975
Macaque monkey (F)	Intravenous injection	Single dose of 3.0 mg/kg on days 21-46 of pregnancy	No adverse effects	Wilson 1971

METHOTREXATE--ANIMAL EVIDENCE (continued)

Species (and Sex)	Route	Exposure Dose and Time	Effect	Reference
Macaque monkey (F)	Intravenous injection	Single dose of 3-4 mg/kg on days 17-21 of pregnancy	Abortion in one of three monkeys	Wilson 1971
Macaque monkey (F)	Intravenous injection	2-4 doses of 3-4 mg/kg on days 18-45 of pregnancy	Abortion in two of six monkeys; malrotation of the gut in one monkey; three monkeys normal	Wilson 1971

METHYLMERCURY--ANIMAL EVIDENCE

Species (and Sex)	Route	Exposure Dose and Time	Effect	Reference
Rat (F)	Oral	Methylmercuric chloride at about 1.4 mg/kg on days 0-20 of gestation	Histopathological changes in cerebellum	Nonaka 1969 as reported by Wilson and Fraser 1977b
Rat (F)	Oral	Dimethylmercuric sulfide at 0.1 mg/kg throughout gestation	Decreased fetal weight, neonatal death, disturbance of postnatal development	Fujita 1969 as reported by Wilson and Fraser 1977b
Rat (F)	Oral	Methylmercuric chloride at 6 or 8 mg/kg on days 7-20 of gestation	Decreased birth weight, decreased litter size	Courtney 1971 as reported by Wilson and Fraser 1977b
Rat (F)	Oral	Methylmercuric chloride at 5 mg/kg on days 0-12 of gestation	Intrauterine death, generalized edema, subcutaneous hemorrhage, brain lesions	Murakami 1972 as reported by Wilson and Fraser 1977b
Rat (F)	Oral	0.002-0.25 mg/kg/day on days 0-21 of gestation	100% stillbirths or neonatal deaths; developmental defects of the eye significant at 0.25 mg/kg/day	Khera and Tabacova 1973
Rat (F)	Intraperitoneal	Methylmercuric chloride at 7.6-11.4 mg/kg on days 8-11 and 14	Eye lesions	Marcus and Becker 1972 as reported by Wilson and Fraser 1977b

METHYLMERCURY--ANIMAL EVIDENCE (continued)

Species (and Sex)	Route	Exposure Dose and Time	Effect	Reference
Rat (F)	Subcutaneous	2-16 mg on days 0-16 of gestation	Increased maternal death, prenatal resorption, fetal death, and decreased fetal weight	Mottet 1974
Mouse (F)	Oral	Methylmercuric chloride at 30 mg/kg once between days 6 and 13 of gestation	Cleft palate, micrognathia, microglossia, brain lesions	Inouye et al. 1972 as reported by Wilson and Fraser 1977b
Mouse (F)	Oral	Methylmercuric chloride at 0.1-2.0 mg/kg on day 10 of gestation	At 0.5 mg/kg and over, intrauterine death and generalized edema	Kawabe et al. 1972 as reported by Wilson and Fraser 1977b
Mouse (F)	Oral	1 mg/kg/day on days 6-18 of pregnancy	Histochemical reactions of DPN diaphorase, inhibition of succinic dehydrogenase and adenosine triphosphate (ATP)	Khera and Nera 1971
Mouse (F)	Oral intubation	Methylmercuric chloride at 0.001-5 mg/kg/day on days 6-17 of gestation	At 1 mg/kg, retarded cerebellar differentiation; at 5 mg/kg, total fetal deaths; developmental defects of the eye	Khera and Tabacova 1973

METHYLMERCURY--ANIMAL EVIDENCE (continued)

Species (and Sex)	Route	Exposure Dose and Time	Effect	Reference
Mouse (F)	Intra-peritoneal	Methylmercuric dicyanodiamide at 4 or 8 mg/kg on day 7 or 9 of gestation	Neonatal death, growth retardation, some neurological and behavioral impairments	Spyker 1972 as reported by Wilson and Fraser 1977b
Mouse (F)	Intra-pertioneal	4 or 8 mg/kg on day 10 of gestation	Embryocidal; high percentage of resorbed fetuses and cleft palate; other malformations, including anophthalmia, micrognathia, excencephaly, missing limbs, and facial deformities	Su and Okita 1976a
Mouse (F)	Intra-peritoneal	Methylmercuric dicyanodiamide at 2, 4, or 8 mg/kg once between days 6 and 13 of gestation	Growth retardation; developmental disturbance; malformations of the brain, palate, and face	Spyker and Smithberg 1972
Mouse (F)	Intra-peritoneal	One dose of methylmercuric hydroxide at 10 mg/kg, with mating 0.5-4.5 days later or pairing with untreated male for 404 days	Reduction in total number of implants and in the number of living embryos; reduction in average number of young born per female	Suter 1975

METHYLMERCURY--ANIMAL EVIDENCE (continued)

Species (and Sex)	Route	Exposure Dose and Time	Effect	Reference
Mouse (M)	Intra-peritoneal	One dose of methyl-mercuric hydroxide at 10 mg/kg, with mating on the next 48 days	Reduction in total number of implants and in the number of living embryos in mated untreated females	Suter 1975
Mouse (M)	Intra-peritoneal	One dose at 1 mg/kg, with mating on the next 7 days	Inhibition of early stages of spermato-genesis; reduced fertility	Lee and Dixon 1975
Mouse (F)	Subcutaneous	6-12 mg/kg on day 10 of gestation	Decreased exploratory behavior; depressed spontaneous locomotor activity; increased susceptibility to con-vulsions	Su and Okita 1976b
Mouse (F)	Subcutaneous	2, 4, or 8 mg/kg on day 10 of gestation	Embryocidal; high percentage of resorbed fetuses and cleft palate; other malformations, in-cluding anophthalmia, micrognathia, excenceph-aly, missing limbs, and facial deformities	Su and Okita 1976a

METHYLMERCURY--ANIMAL EVIDENCE (continued)

Species (and Sex)	Route	Exposure Dose and Time	Effect	Reference
Mouse (F)	Subcutaneous	8-12 mg/kg on day 10 of gestation	Embryocidal; high percentage of resorbed fetuses and cleft palate; other malformations, including anophthalmia, micrognathia, excencephaly, missing limbs, and facial deformities	Su and Okita 1976a
Mouse (F)	Subcutaneous	2-10 mg/kg/day on days 7-12 of gestation	Embryocidal; high percentage of resorbed fetuses and cleft palate; other malformations, including anophthalmia, micrognathia, excencephaly, missing limbs, and facial deformities	Su and Okita 1976a
Mouse (F)	Intravenous	8 mg/kg on day 10 of gestation	Embryocidal; high percentage of resorbed fetuses and cleft palate; other malformations, including anophthalmia, micrognathia, excencephaly, missing limbs, and facial deformities	Su and Okita 1976a

METHYLMERCURY--ANIMAL EVIDENCE (continued)

Species (and Sex)	Route	Exposure Dose and Time	Effect	Reference
Hamster (F)	Intra-peritoneal	Methylmercuric chloride at 8 mg/kg on days 5, 8, or 9 of gestation	Increased incidence of fetal resorptions; decreased fetal weights; malformations, particularly clubfoot and hydrocephalus	Harris et al. 1972
Hamster (F)	Intra-peritoneal	Methylmercuric chloride at 4 mg/kg on day 8 of gestation	No effects	Harris et al. 1972
Hamster (F)	Intra-peritoneal	Methylmercuric chloride at 2 or 4 mg/kg/day on days 1-14 of gestation	At 2 mg/kg, fetal resorptions and such malformations as hydrocephalus, clubfoot, cleft palate, and micrognathia	Harris et al. 1972
Hamster (F)	Intravenous	2-4 mg of mercuric acetate/kg or 5-10 mg of phenylmercuric acetate/kg on day 8 of gestation	Delayed growth rate; increased incidence of resorptions with several malformations, including exencephaly, encephalocele, anophthalmia, microphthalmia, cleft lip and palate, rib fusions, and syndactylia	Gale and Ferm 1971

METHYLMERCURY--ANIMAL EVIDENCE (continued)

Species (and Sex)	Route	Exposure Dose and Time	Effect	Reference
Cat (F)	Oral	Methylmercuric chloride at 0.03-0.25 mg/kg on days 10-58 of induced pregnancy	At 0.25 mg/kg, increased incidence of abortion, fetal anomalies of the visceral and skeletal systems, reduced neuronal population in cerebellum of surviving fetuses; minimal or no embryopathic effects at lower doses	Khera 1973

NICOTINE--ANIMAL EVIDENCE

Species (and Sex)	Route	Exposure Dose and Time	Effect	Reference
White leghorn chickens	Injection into eggs	Various unspecified concentrations of nicotine sulfate at several stages of gestation	Multiple congenital abnormalities, predominantly shortening and twisting of the neck, secondary to abnormal development of cervical spine	Landauer 1960 as reported by USDHEW 1979b
Mice (F)	Injection (site unspecified)	Unspecified doses (critical period, day 6-14 of gestation)	Numerous fetal malformations, including delayed osteogenesis, malformation of major joints, polydactyly, syndactyly, and spinal curvature	Nishimura and Nakai 1958 as reported by USDHEW 1979b
Mice (F)	Injection (site unspecified)	Doses about 15% of amount used by Nishimura and Nakai (1958)	No fetal abnormalities	Landauer 1960 as reported by USHDEW 1979b
Rat (F)	Injection (site unspecified)	3 mg/kg/day throughout gestation	Prolonged gestation	Becker and Martin 1971 as reported by USDHEW 1979b
Rat (F)	Injection (site unspecified)	7.5 mg nicotine tartrate twice daily from proestrus to day 1-5 of gestation	Delayed ovum implantation	Yoshinaga et al. 1979 as reported by USDHEW 1980

NICOTINE--ANIMAL EVIDENCE (continued)

Species (and Sex)	Route	Exposure Dose and Time	Effect	Reference
Rat (F)	Unspecified	(Dose comparable to that of a 20-cigarette/day smoker)	Decreased litter size, increased rate of stillbirths	Hamosh et al. 1979 as reported by USDHEW 1980
Rat (F)	Unspecified	100 mg/kg/day from day 14 through gestation	No effect observed	Hamosh et al. 1979 as reported by USDHEW 1980
Rat (F)	Injection (site unspecified)	"Large doses"	Low birth weight, short crown-rump length, small transverse head diameter, reduced ossification of forelimb bones, short vibrasse, and short claw length	Becker et al. 1968 as reported by USDHEW 1979b
Rats (F)	Injection (site unspecified)	3 mg/kg twice daily throughout gestation	Altered electroshock seizure patterns in newborn rats, which indicate effects on the maturation of the subcortical brain and perhaps other portions of the central nervous system	Hudson et al. 1973 as reported by USHDEW 1979b

POLYCHLORINATED BIPHENYLS (PCBs)--ANIMAL EVIDENCE

Species (and Sex)	Route	Exposure Dose and Time	Effect	Reference
Rat (F)	Oral; in diet	Kanechlor 300 and 500 at 20-500 ppm in diet for entire gestation	Low birth weight	Shiota et al. 1974
Rat (F)	Oral; in diet	Kanechlor 500 at 100 mg/kg on days 8-14 or 15-21 of gestation	Increased abortion, perinatal death, maternal death; suppressed weight gain in offspring	Shiota et al. 1974
Rat (M and F)	Oral; in diet	Aroclor 1254 at 500 ppm in diet from 67 days before mating through lactation	Reductions in number of litters and in litter size, 100% mortality in neonates by day 3	Linder et al. 1974
Rat (M and F)	Oral; in diet	Aroclor 1254 at 1-100 ppm in diet for two generations	Fewer pups in F1b and F2 generation at higher dosage; decreased mating performance from F1b adults	Linder et al. 1974
Rat (F)	Oral	Aroclor 1254 at 6.25-100 mg/kg/day on days 6-15 of gestation	No effects on number or size of litters, on the numbers of dead fetuses or resorptions, or on the incidence of anomalies; at 100 mg/kg, lower average litter weight	Villeneuve et al. 1971

Species (and Sex)	Route	Exposure Dose and Time	Effect	Reference
Mouse (F)	Oral	0.5 mg 2,4',5-tri- or 2,2',4,4',5,5'- hexachlorobenzene/ day on days 1-7 of gestation	Significantly lower implantation rate	Orberg 1978
Mouse (F)	Oral	0.025 mg Clophen A60/day for 10 wk	Lengthening of estrus cycle; decrease in implantation ratio	Orberg and Kihlstrom 1973, Kihlstrom et al. 1973 as reported by Kimbrough et al. 1978
Mouse (F)	Subcutaneous	Clophen A60 at 50 mg/kg on day of parturition and then once a week for 3 weeks	Decreased litter size from F1 parents	Kihlstrom et al. 1975 as reported by Kimbrough et al. 1978
Rabbit (F)	Oral	Aroclor 1254 at 1-50 mg/kg/day for first 28 days of gestation	At 12.5-50 mg/kg, abortions maternal, death, stillbirth and asymmetric skulls in two fetuses; at 1 and 10 mg/kg, no effects detected	Villeneuve et al. 1971
Beagle dog (F)	Oral; in diet	0.25-5 mg/kg/day for entire gestation	Fourfold increase in resportions at 5 mg/kg; sharp increase in patent fontanelles at 1 and 5 mg/kg	Earl et al. 1976 as reported by NIOSH 1977b

PCBs--ANIMAL EVIDENCE (continued)

Species (and Sex)	Route	Exposure Dose and Time	Effect	Reference
Miniature swine (F)	Oral; in diet	1-3 mg/kg/day from 21 days before breeding through gestation	Increased resorption at all levels; teratogenic abnormalities, including cleft palate, syndactyly, and patent fontanelles, at higher dosages	Earl et al. 1976 as reported by NIOSH 1977b
Rhesus monkey (F)	Oral; in diet	Aroclor 1248 at 2.5 and 5.0 ppm in diet for up to 12 mo	Irregular menstrual cycles and excessive, prolonged menstrual bleeding within 4 mo; lower conception rate after 7 mo	Barsotti et al. 1976
Rhesus monkey (F)	Oral; in diet	Aroclor 1248 at 2.5 and 5.0 ppm in diet from 6 mo before mating to 3 mo postpartum	Increased incidence of abortion; low birth weight; pigmentation of skin at birth; decreased infant survival	Allen and Barsotti 1976
Rhesus monkey (F)	Oral; in diet	Aroclor 1248 at 2.5 or 5.0 ppm for up to 14 mo	No observed effect on breeding	Barsotti et al. 1976

THALIDOMIDE--ANIMAL EVIDENCE

Species (and Sex)	Route	Exposure Dose and Time	Effect	Reference
Rat and mouse (F)	Unspecified	Up to 4,000 mg/kg	An increased prevalence of malformations in only a few of some 60 reports of experiments	Nishimura and Tanimura 1976
Mouse (F)	Oral intubation	31 or 62 mg/kg/day	High incidence of congenital abnormalities, including absence of bones of the extremities and scoliosis, particularly with exposure during days 6-8; rate of placental resorption twice that in controls; smaller litters	DiPaolo 1963
Rat (F)	Oral	500 mg/kg/day on days 0-2, 6-8, 7-9, or 9-11 of gestation	Reduction in proportion of successful pregnancies; increased number of resorptions; decreased fetal weight; malformation and malposition of the limbs and tail	Bignami et al. 1962
Rabbit (F)	Unspecified	2.5 mg/kg on days 8-10 of gestation	Limb defects (susceptibility of rabbits to thalidomide shown in some 30 reports)	Schardein 1976

THALIDOMIDE--ANIMAL EVIDENCE (continued)

Species (and Sex)	Route	Exposure Dose and Time	Effect	Reference
Rabbit (F)	Oral	150 mg/kg/day on days 8-16 of gestation	Stillbirths; limb deformities	Somers 1962
Ferret (F)	Unspecified	Unspecified doses at various intervals from days 8-28 of gestation	Cleft palate or lip among 38% of viable offspring; polydactyly in about 12% of fetuses	Steffeck and Verrusio 1972
Armadillo (F)	Oral, in diet	100 mg/kg/day for 10-15 consecutive days during various periods of gestation	Abortion or failure to implant	Marin-Padilla and Benirschke 1963
Swine (F)	Oral, in diet	1 or 100 mg/kg days 17-57 of gestation	No observed effects	Jonsson 1972
Various primates (F)	Oral	5-30 mg/kg on days 18-44 of gestation	High incidence of limb defects	Schardein 1976

TOBACCO SMOKE--ANIMAL EVIDENCE

Species (and Sex)	Route	Exposure Dose and Time	Effect	Reference
Rat (F)	Inhalation	Unspecified amounts during gestation	Sterility, resorption, abortion, neonatal death, reduced birth weight	Essenberg et al. 1940 as reported by USDHEW 1979b
Rat (F)	Inhalation	Unspecified amounts during gestation	Reduced birth weight	Younoszai et al. 1969 as reported by USDHEW 1979b
Mouse (F)	Inhalation	Unspecified amounts during gestation	Reduced maternal weight gain	Wagner et al. 1972 as reported by USDHEW 1979b
Rabbit (F)	Inhalation	Unspecified amounts throughout life	Unsuccessful breeding, stillbirth, neonatal death	Shoeneck 1941 as as reported by USDHEW 1979b
Sheep (F)	Inhalation	Eight or nine cigarettes in 1 hour near term of pregnancy	Minor changes in maternal and fetal blood pressures, heart rates, and blood gases	Kirshbaum et al. 1970 as reported by USDHEW 1979b

NOTE: Also see tables for carbon monoxide and nicotine

VINYL CHLORIDE--ANIMAL EVIDENCE

Species (and Sex)	Route	Exposure Dose and Time	Effect	Reference
Rat (F)	Inhalation	4.8/35.5 mg/m^3 4 hr/day for entire pregnancy	Increased hemorrhages in fetuses; decreased orientation reactions, blood Hb levels, and heart, liver, kidney, and spleen weights in male offspring; increased blood leukocyte levels in females	Sal'niokova and Kitsovskaya 1980
Rat (F)	Inhalation	6.15 mg/m^3 continuously for entire gestation (21 days)	Embryotoxicity; increased fetal mortality; lowered fetal weights; internal and external malformations, such as hydrocephaly and encephalocele; increased hematomas; disturbed skeletal ossification; signs of early toxic hepatopathy in fetuses	Mirkova et al. 1978
Rat (F)	Inhalation	4,000 mg/m^3 (about 1,500 ppm) continuously during 1st third of pregnancy	Increased fetal mortality and embryo toxicity; no effect if exposure during 2nd or last 3rd of pregnancy	Ungvary et al. 1978

VINYL CHLORIDE--ANIMAL EVIDENCE (continued)

Species (and Sex)	Route	Exposure Dose and Time	Effect	Reference
Rat (F)	Inhalation	500 or 2,500 ppm on days 6-15 of gestation	No effects in offspring*	John et al. 1977
Mouse (F)	Inhalation	12,000 mg/m^3 (4,600 ppm) for 5 hr on day 10 of pregnancy	No abnormal morphology	Peter and Ungvary 1980
Mouse (F)	Inhalation	50 or 500 ppm on days 6-15 of gestation	No effects in offspring	John et al. 1977
Rabbit (F)	Inhalation	500 or 2,500 ppm on days 6-15 of gestation	No effects in offspring	John et al. 1977

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WARFARIN--ANIMAL EVIDENCE

Species (and Sex)	Route	Exposure Dose and Time	Effect	Reference
Mouse (F)	Intravenous	3 mg/day on days 6-8 of gestation	40% fewer implantatations than in controls (no difference observed when exposure on days 2-3 or 11-12)	Bergstrom 1971
Mouse (F)	Intra-peritoneal	4 mg sodium warfarin/kg on days 8-11 of gestation	Increased frequency of minor malformations and of fetal death and re-sorption	Kronick et al. 1974
Mouse (F)	Intra-peritoneal	2-4 mg sodium warfarin/kg on days 3-11 of gestation	Placental hemorrhage and subsequent fetal loss	Kronick et al. 1974
Rabbit (F)	Intramuscular	1-3 mg/kg every 2-3 days from day 7 of gestation to term (day 29-30)	100% stillbirths; multiple subcutaneous hemorrhages (100% live births without hemorrhages when exposure on days 7-25 of gestation)	Hirsh et al. 1970
Rabbit (F)	Oral intubation	7-8 mg dicumarol/day on days 5-25 of gestation (dose lowered or withheld some days to maintain prothrombin level)	Fetal and neonatal death; low prothrombin levels in neonates	Kraus et al. 1949
Dog (F)	Oral	Unspecified doses of dicumarol during the last week of gestation	Reversible reduction in prothrombin level in newborn pups	Quick 1946