Fourth Annual Report on

Carcinogens

Summary
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EXECUTIVE SUMMARY

The *Fourth Annual Report on Carcinogens*, prepared by the National Toxicology Program (NTP), U.S. Public Health Service, is issued by the Secretary of the Department of Health and Human Services (DHHS), pursuant to Public Law 95-622 of November 9, 1978.* This law requires the Secretary to publish an annual report which contains "a list of all substances (i) which either are known to be carcinogens or which may reasonably be anticipated to be carcinogens and (ii) to which a significant number of persons residing in the United States are exposed; . . ." Annual reports should also provide available information on the nature of exposures, the estimated number of persons potentially exposed, and the extent to which the implementation of Federal regulations decreases the risk to public health from exposure to these substances.

For the purpose of this Report, "known carcinogens" are defined as those substances for which the evidence from human studies indicates that there is a causal relationship between exposure to the substance and human cancer. Substances "which may reasonably be anticipated to be carcinogens" are defined as those for which there is a limited evidence of carcinogenicity in humans or sufficient evidence of carcinogenicity in experimental animals.

Substances in the above categories, for which potential exposure of persons residing in the United States has been demonstrated, are included in the Report. Also included are some substances which have been banned or the use of which has been restricted because people previously exposed are potentially at risk or because some of these substances still remain in the environment. The *Fourth Annual Report* does not contain all known or reasonably anticipated carcinogens. Additional substances with identified carcinogenic properties as defined above will be included in the subsequent Annual Reports.

Several problems are encountered in developing the information required for the Annual Reports on Carcinogens. Estimating the number of people potentially exposed to a substance and identifying the nature, route, and intensity of the potential exposure are difficult tasks. It is often impossible to obtain accurate production volumes and use patterns for most chemicals. The information that is being collected by the U.S. Environmental Protection Agency under the Toxic Substances Control Act, at least that part which is public record, may assist in obtaining more accurate potential exposure estimates in the future. In addition, the upcoming National Occupational Exposure Survey** will provide new information on the extent and degree of potential exposures for different substances and manufacturing processes.

Perhaps the hardest task in preparing the Report is to evaluate the effectiveness of Federal regulations in decreasing the risk to public health. One

* Section 262 Paragraph (4)

** An update of the National Occupational Hazard Survey conducted from 1972 to 1974 by the Centers for Disease Control/National Institute for Occupational Safety and Health (CDC/NIOSH).

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reason is that virtually all Federal laws concerned with reducing risk have been enacted within the last 15 years. Thus, given the relatively long period between exposure to a carcinogen and the onset of disease, the extent to which the regulations implemented during these 15 years have reduced the risk remains unknown. Another reason is that reliable information on past exposures which could be used as a baseline for estimating future risk reduction is generally not available. Nonetheless, decreasing exposure should be considered as reducing carcinogenic risk even if the reduction cannot be quantified at present.

The Fourth Annual Report lists 148 agents. Included are the entries from the Third Annual Report and 31 additional substances or groups of substances. The new entries were chosen from those designated by the Agencies participating in the preparation of the Report,* from those tested within the National Toxicology Program and the National Cancer Institute Carcinogenesis Bioassay Program,** or from those evaluated by the International Agency for Research on Cancer (IARC), a component of the World Health Organization (WHO), located in Lyon, France.

Of the 148 entries, 24 substances or groups of substances and 5 occupational exposures (etiologic agent(s) unknown) associated with a technological process are listed as "known carcinogens."

Substances

- 4-Aminobiphenyl
- Analgesic mixtures containing phenacetin
- Arsenic and certain arsenic compounds
- Asbestos
- Azathioprine
- Benzene
- Benzidine
- N,N-Bis(2-chloroethyl)-2-naphthylamine (chlornaphazine)
- Bis(chloromethyl)ether and technical grade chloromethyl methyl ether
- 1,4-Butanediol dimethylsulfonate (myleran)
- Certain combined chemotherapy for lymphomas
- Chlorambucil
- Chromium and certain chromium compounds
- Coke oven emissions
- Conjugated estrogens
- Cyclophosphamide
- Diethylstilbestrol
- Melphalan
- Methoxsalen with ultra-violet A therapy (PUVA)
- Mustard gas
- 2-Naphthylamine
- Nickel refining
- Thorium dioxide
- Vinyl chloride

Occupational Exposures

- Hematite underground mining
- Isopropyl alcohol manufacture (strong-acid process)
- Manufacture of auramine
- Rubber manufacture (certain occupations)
- Soots, tars, and mineral oils

One hundred nineteen substances or groups of substances are included because they "may reasonably be anticipated to be carcinogens." Nickel appears in both lists because occupational exposure associated with nickel refining is known to be carcinogenic although specific substances which may be responsible for the carcinogenesis in humans have not yet been identified, and elemental nickel and certain nickel compounds may reasonably be anticipated to be carcinogens.

For each substance or group of substances or occupational exposure associated with a technological process, there is a summary description including a synopsis of the evidence that explains inclusion in the Report. This is followed by a collation of regulatory information received from the participating Agencies.

Among the 148 entries, two are natural substances which are not used or produced commercially: aflatoxins and cycasin. Two are food or cosmetic additives, saccharin and safrole. Safrole has been banned for most uses. The use of saccharin has been continued by Congressional mandate.

Thirteen pesticides are listed: amitrole, Aramite®, arsenical pesticides, 1,2-dibromo-3-chloropropane, hexachlorobenzene, Kepone®, lindane and other hexachlorocyclohexane isomers, mirex, nitrofen, sulfallate, toxaphene, 2,4,6-trichlorophenol, and DDT. Most of these substances have been banned or limited in use.

There are 31 therapeutic substances. Twelve of these are anticancer agents: adriamycin, bischloroethyl nitrosourea, 1,4-butanediol dimethylsulfonate (myleran), certain combined chemotherapy for lymphomas, chlorambucil, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU), cyclophosphamide, dacarbazine, melphalan, nitrogen mustard, procarbazine, and tris(1-aziridinyl)phosphine sulfide. Six are hormonal conjugated estrogens, diethylstilbestrol, estrogens (not conjugated-estradiol-17β, estrone, ethinylestradiol, mestranol), norethisterone, oxymetholone, and progesterone. The remaining 13 are used in other therapeutic applications: analgesic mixtures containing phenacetin, azathioprine, N,N-bis(2-chloroethyl)-2-naphthylamine, iron dextran complex, methoxsalen with ultra-violet A therapy (PUVA), metronidazole, phenacetin, phenazopyridine hydrochloride, phenytoin, propylthiouracil, reserpine, selenium sulfide, and streptozotocin.

Two of these other therapeutics are no longer produced or used in the United States: N,N-bis-(2-chloroethyl)-2-naphthylamine and streptozotocin. Five of the anticancer agents also are no longer produced but are imported into the U.S.: adriamycin, chlorambucil, cyclophosphamide, daberbazine, and melphalan. Six of the anticancer agents are imported and produced in limited quantities by one U.S. manufacturer: bischloroethyl nitrosourea, 1,4-butanediol dimethyl sulfonate, 1-(2-chloroethyl)-3-

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* Centers for Disease Control/National Institute for Occupational Safety and Health (CDC/NIOSH), Consumer Product Safety Commission (CPSC), U.S. Environmental Protection Agency (EPA), Food and Drug Administration (FDA), National Institutes of Health/National Cancer Institute (NIH/NCI), National Institutes of Health/National Institute of Environmental Health Sciences (NIH/NIEHS), National Institutes of Health/National Library of Medicine (NIH/NLM), and U.S. Department of Labor/Occupational Safety and Health Administration (DOL/OSHA).

** Now part of NTP/NIEHS.

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cyclohexyl-1-nitrosourea, nitrogen mustard, procarbazine, and tris (1-aziridinyl) phosphine sulfide.

The remaining 95 substances may be classified as various industrial chemicals and byproducts (33); dyes, dye intermediates, and pigments (20); combustion products (14); solvents (7); metals and metal compounds occurring in mining, extraction, and refining processes (6); analytical and research chemicals (6); and chemicals used for miscellaneous purposes (9).

The five occupational exposures (etiological agents(s) unknown) associated with a technological process known to be carcinogenic are those associated with hematite underground mining, isopropyl alcohol manufacture (strong-acid process), manufacture of auramine, rubber manufacture (certain occupations), and soots, tars and mineral oils.

Scientific knowledge and judgment play important roles in grading the available evidence of carcinogenicity as sufficient, limited, or inadequate. Similarly, in all but one category of substances, regulatory action is an interpretation by the regulators of their Congressional mandates. The only mandated exception is the deliberate addition of additives and colors to foods. The Delaney Clause in the Food Additives Amendment of 1958 to the Federal Food, Drug, and Cosmetic Act requires that "no additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animals. . . ."[1]

Corrections or suggestions, as well as any additional information that the reader may have should be sent to the Director, National Toxicology Program, P.O. Box 12233, Research Triangle Park, North Carolina 27709. Summaries of this Report may be obtained from the Public Information Office, National Toxicology Program, B2-04, P.O. Box 12233, Research Triangle Park, North Carolina 27709. Copies of the complete Report are available for a fee from the National Technical Information Service, 5285 Port Royal Road, Springfield, Virginia 22161. Request number PB 85-134833 should be indicated.

[1] So far only two substances have been banned on the basis of the Delaney Clause. Posted H in 1957 and chlorinated in 1959. According to the FDA, both substances were used to make adhesives for food packaging material.

INTRODUCTION

Cancer is the second most common cause of death in the United States. One in every four Americans will suffer from cancer sometime during their lifetime; one in every five will die from cancer. In 1983, more than 440,000 Americans died of cancer.[1] In addition to the physical and emotional suffering caused by cancer, this disease may cost the Nation as much as $39 billion each year in lost production and income, medical expenses, and research resources. For these reasons, the American public is concerned about cancer and cancer hazards, especially about ways to prevent the occurrence or decrease the incidence of cancers.

Contrary to popular belief, cancer is not one but many diseases which may have different causes. Most scientists now consider that about one-third to two-thirds of all cancers are associated with the environment in which we live and work. In this context, the environment is understood as "anything that interacts with humans, including substances eaten, drunk, and smoked, natural and medical radiation, workplace exposures, drugs, aspects of sexual behavior, and substances in air, water, and soil."[2] Some cultural and behavioral patterns, apart from defined habits of smoking and alcohol consumption, may significantly influence the development of tumors in the gastrointestinal tract, breast, uterus, and prostate. These aspects of social environment, personal behavior, and habits are sometimes called "lifestyle." Although we rarely know the environmental factors and conditions which are responsible for the development of specific cancers, in some cases we are beginning to have some understanding. Most cancers that are associated with the environment should be avoidable, at least potentially.

Development of cancer also depends on "host factors." Host factors are attributes of human organisms associated with individual differences in the risk of developing a specified cancer. A host factor may be associated with reduced risk of a cancer, not only with increased risk.[3] Examples of host factors are immunological and endocrine functions, nutritional status, genetic constitution, age, and sex.[4]

As Americans have become more and more concerned about the environment and cancer, they have repeatedly asked the Federal Government to clarify what is known about cancer-causing substances. The public wants to know and should know which substances are regarded as cancer hazards in the work place and in the general environment and how well we are protected from exposure to these substances.

Section 282 of Public Law 95-622 of November 9, 1978[5] reflects the requests for this information. Paragraph (4) of this section stipulates that the "Secretary shall publish an annual report which contains—

> "(A) a list of all substances (i) which either are known to be carcinogens or may reasonably be anticipated to be carcinogens and (ii) to which a significant number of persons residing in the United States are exposed;

[4] Community Mental Health Centers Act Amendments

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"(B) information concerning the nature of such exposure and the estimated number of persons exposed to such substances;

"(C) a statement identifying (i) each substance contained in the list under subparagraph (A) for which no effluent, ambient, or exposure standard has been established by a Federal agency, and (ii) for each effluent, ambient, or exposure standard established by a Federal agency with respect to a substance contained in the list under subparagraph (A), the extent to which, on the basis of available medical, scientific, or other data, such standard, and the implementation of such standard by the agency, decreases the risk to public health from exposure to the substance. "

Annual Reports on Carcinogens are issued in response to these requirements. These Reports discuss individual substances, mixtures of chemicals or exposures associated with technological processes which are known to be carcinogens or which may reasonably be anticipated to be carcinogens; they contain information received from Federal agencies participating in the preparation of the Reports.

Participants

Within the Department of Health and Human Services, the responsibility for preparing these Annual Reports has been given to the National Toxicology Program.* Other agencies participating in the effort are

Centers for Disease Control/National Institute for Occupational Safety and Health (CDC/NIOSH)

Consumer Product Safety Commission (CPSC)

U.S. Environmental Protection Agency (EPA)

Food and Drug Administration (FDA)

National Institutes of Health/National Cancer Institute (NIH/NCI)

National Institutes of Health/National Institute of Environmental Health Sciences (NIH/NIEHS)

National Institutes of Health/National Library of Medicine (NIH/NLM)

U.S. Department of Labor/Occupational Safety and Health Administration (DOL/OSHA)

Four of these agencies—CPSC, EPA, FDA, and OSHA—are responsible for regulating hazardous substances and limiting the exposure to and use of such substances.

Identifying Carcinogens

For many years Government research agencies, industries, universities, and other research organizations have studied various substances to ascertain those which might cause cancer. Other Federal agencies have been developing information on possible exposure and potential hazards and making rules and regulations to control substances which have been identified as carcinogens.

The largest single national testing effort, the National Cancer Institute's Carcinogenesis Testing Program, has now

* DHHS agencies participating in NTP are NIH/NCI, NIH/NIEHS, FDA/National Center for Toxicological Research (FDA/NCTR), and CDC/NIOSH.

became a part of NTP/NIEHS. The NCI Clearinghouse on Environmental Carcinogens, consisting of a panel of experts from governmental and nongovernmental institutions, was reviewing the NCI testing results, and an analysis of results of NCI carcinogenesis bioassays of 180 chemicals was published.[1] The Technical Reports Review Subcommittee of the NTP Board of Scientific Counselors, augmented by an ad hoc panel of experts in chemical carcinogenesis, has replaced the NCI Clearinghouse as the body of nongovernment experts conducting peer reviews of the NTP carcinogenesis bioassay results.

Many of the substances, mixtures of chemicals, and occupational exposures discussed with some technological processes listed in the Fourth Annual Report on Carcinogens have been chosen from the "IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans" published by the International Agency for Research on Cancer (IARC) in Lyon, France.* Each monograph is the product of an individual working group of experts in chemical carcinogenesis and related fields. The experts evaluate the data for each substance included in a monograph. The evaluation is based on the published information available at the time the working group was convened. A joint IARC/WHO ad hoc working group met in October 1977 to review and revise the criteria for judging the adequacy of available data. The terms 'sufficient evidence' and 'limited evidence' of carcinogenicity used in these criteria refer only to the amount and adequacy of the available evidence and not to the potency of carcinogenic effect or the mechanisms involved. An updated version of these criteria is included in each IARC Monograph Volume. The IARC Monograph Supplement 4 contains reevaluations by an ad hoc working group of all chemicals, industrial processes and occupational exposures for which some data on carcinogenicity in humans are available either in the first 29 volumes of monographs or in other subsequent publications.[2] For the most part human data are discussed only for those in the Report that have been re-evaluated in IARC Monograph Supplement 4.

A direct comparison of the IARC evaluations[2] and the evaluation of NCI/NTP bioassay results[3] cannot be made because different criteria were used to assess the evidence, but these criteria can be related.[3] All such evaluations involve a component of personal judgment. In some cases the available evidence may be assessed differently depending on the criteria used and the composition of the group of experts. Thus according to an OTA correlative interpretation of their IARC equivalents, classes 1 and 2 in the NCI classification may be regarded as sufficient evidence in animals; carcinogens.[3,4]

Clause (i) in subparagraph (A)(4) of Section 262 requires "a list of all substances which are either known to be carcinogens or may reasonably be anticipated to be carcinogens." For the purposes of this Report, the two categories in the law—those substances known to be

* The IARC address is: 150, cours Albert Thomas, 69372 Lyon Cedex 2, France. IARC publications may be obtained from: WHO Publications Centre USA, 49 Sheridan Avenue, Albany, New York 12210.

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[illegible] exposed to be carcinogens—relate to the IARC criteria for the degree of evidence[8] as follows:

1. Known to be carcinogens:
   There is "sufficient evidence of carcinogenicity" from studies in humans "which indicates a causal relationship between the agent and human cancer."
2. Reasonably anticipated to be carcinogens
   A. There is "limited evidence of carcinogenicity" from studies in humans "which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias or confounding, could not adequately be excluded," or
   B. There is "sufficient evidence of carcinogenicity" from studies in experimental animals "which indicates that there is an increased incidence of malignant tumors: (a) in multiple species or strains, or (b) in multiple experiments (preferably with different routes of administration or using different dose levels), or (c) to an unusual degree with regard to incidence, site or type of tumor, or age at onset. Additional evidence may be provided by data concerning dose response effects, as well as information on mutagenicity or chemical structure."

Most of the substances contained in the Annual Report can be identified chemically. Some carcinogens occur naturally, some are produced when materials are burned, and others are present in raw materials, or in intermediate and final products of industries. In some cases only the exposure associated with a specific technological or manufacturing process, occupation or industry, or a therapeutic treatment can be related to an increased incidence of cancer in humans, but the substance(s) specifically responsible cannot be identified. Some examples of such technological processes are the underground mining of hematite and the strong-acid process for the manufacture of isopropyl alcohol.

The reader is reminded that the *Fourth Annual Report on Carcinogens* (and all previous editions) is a condensation of large amounts of data and conclusions made by bodies which peer review the data submitted as evidence about cancer and its relation to specific exposures. As such, the *Fourth Annual Report on Carcinogens* must be less detailed about the actual tests and their drawbacks. The original monographs on each listing are given in the footnoted references and the reader is advised to turn to these for specific arguments, both pro and con, which went into the listing decision.

Human and Animal Studies

Some understanding of the human and animal studies used for identifying carcinogens is necessary to clarify what is meant by the words "known" and "reasonably anticipated." The strongest evidence for a relationship between exposure to a suspected substance and cancer in humans comes from epidemiological studies. Although we have adequate epidemiological evidence only for a few carcinogens, we think the patterns seen in these studies show how other animal carcinogens might affect humans. Epidemiological investigations give the best information on cancer-causing agents, but such studies of groups of individuals do have shortcomings. They may require observations over a long time because the latent period between initial exposure and cancer occurrence may be up to 20-30 years. Intentional, long-term exposures of human groups are, of course, unacceptable. As an alternative, qualified scientists make educated predictions about the effects in humans, based on the effects observed in studies with experimental animals.

Although test animals may respond differently from humans, experience has shown that most known human carcinogens also cause cancer in experimental animals if adequately tested.* This finding is understandable since cancer begins in individual cells and all mammalian cells are comparable in structure and function. The basic premise of experimental carcinogenesis research is that substances which produce cancer in rodents and other experimental animals affect human cells in a similar way.

Relatively large doses of chemicals are used in animal studies to compensate for the small number of experimental animals exposed as compared to the size of human populations and also to optimize the potential response. Animal tests are costly, take years to complete, and are often difficult to interpret in terms of human cancer risk. They are, nevertheless, the best testing tool we have for detecting potential hazards.[9,10] Animal tests do not prove beyond doubt that a substance will or will not cause cancer in humans. Even "sufficient evidence" of carcinogenicity in experimental animals may prove not to be definitive. But if we are to prevent cancer, we cannot wait 20 to 30 years to obtain definitive evidence of harm to human health. Therefore, substances which show "sufficient evidence" of cancer causation in experimental animals are considered for practical purposes as reasonably anticipated human carcinogens.

Inclusion of Substances

The *Fourth Annual Report* contains substances, groups of substances and exposures associated with technological processes which were listed in the *Third Annual Report*. Where necessary, the information has been updated. The *Fourth Annual Report* presents information on 31 additional substances. Each has been chosen either from substances tested by the NCI Carcinogenesis Testing Program or the National Toxicology Program (NTP), from designations of the participating agencies, or from substances evaluated by the IARC working groups. Other substances from the same source will be added to subsequent Annual Reports.

The Summary of the Fourth Annual Report lists all the substances and technological processes included. The list is divided into two subsets. One contains substances, groups of substances, or technological processes known to be

* The evidence for carcinogenicity in experimental animals of organic compounds should now be regarded as limited, and the evidence for benzene is at present limited.[9] More recent data would make benzene a sufficient evidence animal carcinogen (see benzene, p. 34). Both of these compounds are known sufficient evidence human carcinogens.

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carcinogens (29 entries). The other list of 119 entries includes substances or groups of substances which may reasonably be anticipated to be carcinogens. Nickel appears in both sublists because the nickel refining process is known to be carcinogenic, whereas elemental nickel and certain nickel compounds may reasonably be anticipated to be carcinogens.

A substance not listed in the Annual Report may still be a known carcinogen or a reasonably anticipated carcinogen. More substances than those included may potentially present a carcinogenic risk to persons living in the United States. These substances will be incorporated into subsequent Annual Reports as resources permit. Some chemicals will be included as a result of testing performed by industry in response to EPA's requests under the Toxic Substances Control Act. The National Toxicology Program will also provide new information for these reports as further test results become available.

Ionizing radiation, ultraviolet radiation (including sunlight), tobacco, alcoholic beverages, and some viruses are known or suspected to be carcinogens. They have not been included in this Report (unless acting in conjunction with a chemical) because ionizing radiation is discussed thoroughly in a General Accounting Office report[8] and a recent Surgeon General's report[9] reviews the overwhelming relationship between tobacco and cancer. Several publications issued by the National Cancer Institute[10] explain the relationship of alcoholic beverages, ultraviolet radiation, and viruses to cancer.

Certain manufacturing processes have also been considered by the International Agency for Research on Cancer (IARC) and have been classified by the Agency as sources of exposure which are associated with increased incidences of cancer in workers in these settings. Among these are Boot and Shoe Manufacture and Repair, and Furniture Manufacture. The IARC reports dealing with these processes are given in the references at the end of the introduction,[11] and the interested reader is referred to these documents for details. These processes were believed by IARC to constitute exposures which caused cancer in some humans and in some settings.[11] The National Toxicology Program does not disagree with these judgments. However, these processes are not listed separately in this Report since neither the specific causes of the cancers nor the specific steps in the processes have been identified. Further, IARC has recognized that these two manufacturing processes vary significantly from one country to another, and that the likelihood is great of variation in exposures to whatever causes the cancers that are seen. These manufacturing processes have also changed significantly in several countries over the last few years, particularly with regard to the mix of chemicals, etc. (used in the various steps of the process) which could be the putative carcinogens.[11]

Estimating Exposure

According to clause (ii) of subparagraph (4)(A), the Report is required to include those substances "to which a significant number of people residing in the United States are exposed." Substances to which only a few people are exposed are not included for the most part. Yet some substances which have been banned or restricted in use are contained in the Report (e.g., telrole, arsenical pesticides, mirex) either because people who were previously exposed remain potentially at risk, or because these substances are still present in the environment.

Subparagraph (4)(B) requires that the Annual Reports provide "information concerning the nature of such exposure and the estimated number of persons exposed to such substances." The determination of the number of people potentially exposed and the route, intensity, and duration of such exposure for each substance remains a formidable task. This Report attempts to respond to these questions, and wherever adequate answers could be obtained, they are included in Sections IIIB and IIIC. Exposure to carcinogens can occur anywhere. Some carcinogens have always been present in the environment, and their amount varies, depending on geographical location and other environmental conditions. Every year human activities may add more carcinogens to the ambient air, water, food, soil, and occupational environment. Although scientists attempt to estimate the amount of carcinogens present in and added to the environment, there is no reliable way to predict who is exposed to what carcinogen and when exposure occurs. Also, since human populations are always exposed to many chemicals at the same time, this may modify the effects of a specific exposure either by multiplying (synergism) or reducing its action (antagonism).

If exposure is linked to a specific habit such as smoking, a specific use such as medical diagnosis or treatment, or a restricted environment such as the workplace, our ability to estimate exposure improves, and in some cases the size of population segments involved can be estimated. Production and use data may also help estimate possible exposure, but the information may not be publicly available for many substances and where it is, it may be outdated or even contradictory.

The National Occupational Hazard Survey (NOHS), conducted by CDC/NIOSH from 1972 to 1974, gave information on the number of workers potentially exposed and on some broader aspects of potential occupational exposure. The forthcoming National Occupational Exposure Survey (a repeat of NOHS) should yield valuable information with respect to more recent possible exposures. Subsequent Annual Reports on Carcinogens will explore this and other available data bases, and their strengths and limitations.

Regulatory Status

Subparagraph (4)(C) of Section 262 also requires "a statement identifying (i) each substance contained in the list under subparagraph (A) for which no effluent, ambient, or exposure standard has been established by a Federal agency." The Fourth Annual Report responds to the requirement by appending to the description of each substance a summary of Federal regulations as submitted by the participating agencies. Some of these standards and regulations have been enacted for reasons other than the carcinogenicity of the substance (or instance, to prevent other adverse health effects or to improve the quality of the environment or food. Solid or liquid wastes or wastes discharged into the air may contain carcinogens, yet these may

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be regulated as toxic substances or hazardous pollutants and not specifically as carcinogens. But if these regulations reduce exposure to carcinogens, then the cancer risk posed by such substances will also decrease.

Estimating Risk Reduction

Clause (ii) in subparagraph (4)(C) requires a statement identifying "for each effluent, ambient, or exposure standard established by a Federal agency with respect to a substance contained in the list under subparagraph (A), the extent to which, on the basis of available medical, scientific, or other data, such standard, and the implementation of such standard by the agency, decrease the risk to public health from exposure to the substance;". This requires quantified information on the amount of protection from cancer the public receives from established Federal standards.

Estimating the amount of health protection is perhaps the most difficult task in preparing the Annual Reports. One reason is that most Federal laws concerned with reducing cancer risk have been enacted within the last 15 years. Given the long period between the initial exposure to a carcinogen and the onset of disease, it is still too early to evaluate how much Federal standards and other regulations have decreased the human cancer risk. Another reason is that information on past exposure levels, which could serve as a baseline for estimating future risk reduction, often is not available or accurate.

The risk — the probability of developing cancer — depends on the intensity, route, and duration of exposure to a carcinogen. Individuals may respond differently to similar exposures, depending on host factors such as age, sex, nutritional status, overall health, and inherited characteristics. Only in a few instances, where studies of long-term human exposures and cancer incidence in restricted environments are available, can risk be estimated with confidence.

The regulation of asbestos in the workplace provides a good example. In 1969, under the Walsh-Healey Act, which then regulated only the firms with Government contracts, the standard for permissible exposure was 12 fibers of asbestos per cubic centimeter (cm^3) of air. Under the Occupational Safety and Health Act, the standard was reduced to 5 fibers/cm^3 in 1972 and to 2 fibers/cm^3 in 1976. On April 17, 1980, a joint NIOSH-OSHA Working Group recommended the elimination of all nonessential uses of asbestos and the implementation of a public health program to reduce human exposures. On April 10, 1984, OSHA proposed a rule lowering the permissible exposure to 0.2 or 0.5 fibers/cm^3 (5 micrometers in length) and requiring other provisions for employee protection. The high risk in workers exposed prior to 1969 is well known. The actual data on exposure levels in the '40s, '50s, and '60s are fragmentary, although exposure levels were undoubtedly unacceptably high by today's standards. Mesothelioma (primarily an asbestos-induced cancer) and lung and other cancers, the incidence of which is increased by exposure to asbestos, generally take 20-40 years or more to develop and become apparent. For these reasons, we will not know until early in the next century to what extent the series of exposure reductions in the '70s and '80s have reduced the cancer risk in persons exposed to asbestos.

One possible way to provide quantitative estimates of risk reduction might be to assume that the cancer risk is directly proportional to exposure. This approach also supposes that data on past and present exposure levels are available, or that conditions in all workplaces are in compliance with regulations. However, information supporting these assumptions is only rarely obtainable. Nevertheless, it is reasonable and prudent to accept that the reduction of exposure, for any reason, particularly to substances shown to be carcinogenic in experimental animals, will decrease the incidence of cancer.

This is the basis of current regulatory policies which aim to lower human exposure to cancer-causing substances and thereby improve public health. For a more detailed discussion of the issues involved, see the previously cited report to Congress on the assessment of technologies for determining cancer risks from the environment.[2]

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Department of Health and Human Services, Public Health Service, 1982.
10. See, for example, Shimkin, M.B. Science and Cancer. NIH Publications No. 80-588, Third Revision. National Cancer Institute, National Institutes of Health. Bethesda, Maryland: U.S. Department of Health and Human Services, 1980.
11. International Agency for Research on Cancer (IARC). Wood, Leather and Some Associated Industries. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Volume 25. 412 pp. Lyon, France: IARC, 1981, pp. 99-139, 249-277.

2-ACETYLAMINO-FLUORENE

CARCINOGENICITY

Incorporation of this compound into the feed caused increased incidences of malignant tumors in a variety of organs in the rat.[1] Long-term studies in which mice were given 2-acetyl-aminofluorene (AAF) in the diet showed increased incidences of liver and urinary bladder cancers.[2]

PROPERTIES

AAF occurs in the form of crystalline needles. It is insoluble in water.

USE

AAF is used as a positive control by toxicologists to study the carcinogenicity and mutagenicity of aromatic amines. AAF was intended for use as a pesticide, but was never marketed because it was carcinogenic in experimental animals.

PRODUCTION

AAF is imported from Europe and distributed by several specialty chemical companies. A typical distributor stocks about 10 pounds of AAF and usually sells it in 1-, 5-, or 25-gram quantities. Total estimated U.S. usage is less than 20 pounds per year.

The 1979 TSCA Inventory reports one producer but no production volume.[3]

EXPOSURE

Human exposure to AAF may occur through inhalation and skin absorption. People who face the greatest risk to AAF exposure are chemists, chemical stockroom workers, and biomedical researchers. Although neither NIOSH nor OSHA estimated the number of U.S. workers exposed to this animal carcinogen, it may be fewer than 1,000 in 200 laboratories that are possibly exposed.

REGULATIONS

EPA regulates AAF under the Resource Conservation and Recovery Act and the Comprehensive Environmental Response Compensation and Liability Act. Because AAF is carcinogenic in animals, OSHA promulgated a standard for the chemical on February 11, 1974, designating protective clothing, hygiene procedures for workers, and special engineering requirements for the manufacture or processing of AAF.

ACRYLONITRILE

CARCINOGENICITY

There is sufficient evidence for the carcinogenicity of acrylonitrile in experimental animals.[4] Acrylonitrile was carcinogenic in rats when administered

[1] Wilson, R.H., F. DeEds, and A.J. Cox. The Toxicity and Carcinogenic Activity of 2-Acetylaminofluorene. Cancer Res. Vol. 1, 1941, pp. 595-602.
[2] Stoltz, J.A., and M.A. Mehlman, eds. Innovations in Cancer Risk Assessment (ED$_{01}$ Study): Proceedings of a Symposium. J. Environ. Pathol. and Toxicol. Vol. 3, 1980, pp. 1-240.

[3] Toxic Substances Control Act. Chemical Substance Inventory, 1979, public record.
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PRODUCTION

According to NCI, the U.S. production of decabromobiphenyl reported to the U.S. International Trade Commission was greater than 10,000 pounds for 1980. The 1979 TSCA inventory identifies one company producing an undisclosed amount of hexabromobiphenyl.[440] Earlier, EPA also reported one U.S. producer of PBBs.[440] Production of some PBBs ceased in the late 1970's. CPSC reported that the sole U.S. manufacturer of hexabromobiphenyl ceased production in 1974 and held the remaining stock of the product until the supply was exhausted in April, 1976. From 1970 to 1974, about 11 million pounds of hexabromobiphenyl were manufactured by a single U.S. company and marketed under the trade names Firemaster BP-6 and Firemaster FF-1. Commercial production of PBBs began in 1970.

EXPOSURE

FDA stated that potential human exposure to PBBs is through ingestion of foods containing PBB residues. Present sources of PBBs seem to be residues remaining in and around plants that formerly manufactured, processed, or produced products using PBBs. In 1974, the National Occupational Hazard Survey estimated that 4,800 workers were possibly exposed to PBBs. For example, workers in one company that manufactured PBBs were possibly exposed directly to PBBs by skin contact, inhalation, and unintensional ingestion; investigators detected 1.1 to 1,729 ppb of hexabromobiphenyl in the workers' sera and 0.51 to 581 ppm in their adipose tissue.

REGULATIONS

The category of PBBs, potentially containing up to 200-300 individual chemicals, is subject to a special TSCA 8(a) reporting rule. EPA has proposed handling and reporting/recordkeeping requirements for PBBs under the Resource Conservation and Recovery Act. Under section 408 of the Food, Drug, and Cosmetic Act, FDA regulates PBB compounds as unavoidable environmental contaminants. In cooperation with the Centers for Disease Control and the Public Health Department of the State of Michigan, FDA monitors the long-term human health effects from acute exposure to PBBs.

POLYCHLORINATED BIPHENYLS

CARCINOGENICITY

The evidence for carcinogenicity of polychlorinated biphenyls (PCBs) in experimental animals is sufficient.[441] Certain mixtures of PCBs (e.g., Kanechlor 500, Aroclor 1254 and 1260) were carcinogenic in mice and rats after administration in the diet, producing liver tumors.[442,443] PCB (1260) was carcinogenic in the female rat, also producing liver tumors.[442]

The evidence for the carcinogenicity of PCBs in humans is inadequate.[441] A slight increase in the incidence of cancer, particularly melanoma of the skin, has been reported in a small group of men exposed occupationally to Aroclor 1254, a mixture of PCBs.[441]

PROPERTIES

PCBs vary in appearance from mobile, oily liquids to white crystalline solids to hard, noncrystalline resins. All forms are insoluble in water.

USE

Since 1974, all uses of PCBs in the United States have been confined to closed systems. Before 1972, PCBs were used in transformer cooling liquids, heat-transfer and hydraulic fluids, vacuum pump fluids, lubricants, plasticizers, fillers in investment casting waxes, surface coatings and sealants, pesticide extenders, and copy paper.

PRODUCTION

The 1979 TSCA inventory identifies one company producing 35,585,500 pounds of PCBs.[444] PCBs are no longer produced in the United States, except for limited research and development applications; import and export of the compounds has not been permitted since July, 1979. Prior to 1977, annual domestic production of PCBs was about 35 million pounds. Domestic production reached a peak volume of 86 million pounds in 1970 and decreased to about 41 million pounds by 1974. PCBs first were produced in the United States in 1929.

EXPOSURE

The release of PCBs from prior industrial uses and the persistence of the compounds in the environment have resulted in widespread contamination of water and soil, with subsequent potential exposure of the general population. Routes of exposure include skin absorption and ingestion; a major source of exposure is through the diet. A 1971 report indicated that fish, cheese, eggs, and contaminated animal feed were in major U.S. commodities in which PCBs were found. The percentage of food samples contaminated with PCBs decreased between 1973 and 1975. Residues of PCBs have been detected in human milk and fat samples collected from the general U.S. population. EPA reports that about 12 million persons within 12 miles of three existing and ten projected commercial incinerators may possibly be exposed to releases of PCBs.

REGULATIONS

In 1970, EPA banned PCBs as a pesticide ingredient and canceled registration of products containing PCBs. EPA promulgated toxic pollutant effluent standards in 1977 and modified its marking and disposal rule in 1979, which was effective in identifying and eliminating some PCB sources in 1979. EPA issued a ban on manufacturing

[440] Toxic Substances Control Act. Chemical Substance Inventory. 1979 public record.

[441] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. 366 pp. Lyon, France: IARC, 1982. pp. 217-219.

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[443] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. 366 pp. Lyon, France: IARC, 1974. pp. 261-269.

[444] Toxic Substances Control Act. Chemical Substance Inventory. 1979 public record.

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processing, and distributing PCBs in commerce; most manufacturing ceased voluntarily before these rules were issued. EPA proposed a water quality criteria document that will protect freshwater, saltwater, and aquatic organisms, as well as human health. PCBs are regulated as hazardous wastes under the Resource Conservation and Recovery Act and the Comprehensive Environmental Response Compensation and Liability Act. EPA recently assessed air pollution sources of PCBs and is considering the need for regulation of emissions from incinerators, the only source for which controls may be essential. Under the Safe Drinking Water Act, EPA is preparing a report to Congress on the nature and extent of PCB contamination, as well as recommendations for further regulatory action, if necessary.

In 1973, FDA established tolerances for PCBs in several foods and in feeds for food-producing animals. In 1979, four of those tolerances were reduced. The tolerances now are 1.5 ppm (fat basis) in milk and manufactured dairy products, 3 ppm (fat basis) in poultry, 0.3 ppm in eggs, 0.2 ppm in finished animal feed, 2 ppm in animal feed components of animal origin, 5 ppm in fish and shellfish (edible portion), and 0.2 ppm in infant and junior foods. FDA has lowered the PCB standard in fish and shellfish from 5 ppm to 2 ppm and has established action levels of 3 ppm (fat basis) in red meat and 10 ppm in paper food-packaging material. OSHA adopted a standard of 1 mg/m^3 (an 8-hour time-weighted average) for PCBs containing 42 percent chlorine, and 0.5 mg/m^3 for PCBs containing 54 percent chlorine. OSHA adopted these standards for toxic effects other than cancer

PROCARBAZINE AND PROCARBAZINE HYDROCHLORIDE

CARCINOGENICITY

There is sufficient evidence for carcinogenicity in humans of intensive chemotherapeutic regimens that include alkylating agents, vinca alkaloids, procarbazine hydrochloride, and prednisone. There is inadequate evidence for carcinogenicity of procarbazine hydrochloride alone in humans.

There is sufficient evidence for the carcinogenicity of procarbazine in experimental animals.[446-447] Laboratory exposure of animals to procarbazine was studied by intraperitoneal injection. In rats, lymph system cancers and cancers of the mammary gland and olfactory nerve were induced in statistically significant numbers. In mice, cancers of the lymph system or leukemia, cancers of the olfactory nerve, pulmonary neoplasms, and cancers of the uterus were induced in statistically significant numbers.[446]

Evidence of carcinogenicity was also found in mice and rats following administration by gavage; in rats following intravenous administration and in one instance following transplacental exposure. Two studies in two species of nonhuman primates suggest that procarbazine hydrochloride may also produce leukemia when administered by multiple routes to the same animal.[446]

PROPERTIES

Procarbazine is a white to pale yellow crystalline powder that is soluble but unstable in water and aqueous solutions.

USE

Procarbazine hydrochloride is used mainly as an antineoplastic agent to treat Hodgkin's disease and oat-cell carcinoma of the lung. FDA approved its use in 1968, indicating that the drug should be used as an adjunct to standard therapy.

PRODUCTION

The 1979 TSCA Inventory reports no production data for procarbazine and its hydrochloride.[446]

EXPOSURE

Possible exposure to procarbazine and its hydrochloride occurs during manufacture of the drug; direct exposure occurs during administration of procarbazine hydrochloride to patients. In 1981 the National Prescription Audit reported 1.5 million prescriptions dispensed for the drug. Some of the metabolites of procarbazine are both carcinostatic and carcinogenic.

REGULATIONS

There is no indication that procarbazine and procarbazine hydrochloride pose a waste or pollution problem and therefore, EPA has little interest in their regulation. Procarbazine hydrochloride is subject to FDA prescription drug labeling requirements.

PROGESTERONE

CARCINOGENICITY

There is sufficient evidence that progesterone is carcinogenic in experimental animals.[446] Progesterone was tested by subcutaneous and intramuscular injection in mice, rats, rabbits, and dogs and by subcutaneous implantation in mice and rats. In mice and dogs, progesterone was tested alone; in rats and rabbits, it was given in combination with other chemicals. When given alone, progesterone increased the incidence of ovarian, uterine, and mammary tumors in mice. In female mice, treatment of newborn animals with progesterone enhanced the occurrence of precancerous and cancerous lesions of the genital tract and increased mammary tumorigenesis.[446] Dogs treated with progesterone for four years developed a dose-related incidence of mammary gland neoplasms.[446-448]

Administration of progesterone in combination with known carcinogens in mice, rats, and rabbits, affected the

[446] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 26. 411 pp. Lyon, France: IARC, 1981. pp. 311-339.

[447] National Cancer Institute. Bioassay of Procarbazine for Possible Carcinogenicity. Technical Report Series No. 19. DHHS Publication No. (NIH) 79-819. 124 pp. Bethesda, Maryland: 1979.

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