Third Annual Report on

# Carcinogens

Summary
September, 1983

NTP 82-330

This summary of the Third Annual Report on Carcinogens is published by the National Toxicology Program Public Information Office. The individual entries for the cancer-causing agents contained in this summary are reproduced from the Third Annual Report on Carcinogens.

Copies of the Third Annual Report on Carcinogens are available for a fee from the National Technical Information Service, Springfield, Virginia 22161. Specify: PB-83-135855. Phone: (703) 487-4650.

For additional copies of this booklet, contact: NTP Public Information Office, MD B2-04, Box 12233, Research Triangle Park, NC 27709. Phone: (919) 541-3991.

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
Public Health Service

# Contents

Agents in italics are new to this Report

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 Third Annual Report lists 117 agents. Included are the entries from the Second Annual Report and 28 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 part of the World Health Organization (WHO), located in Lyon, France.

Of the 117 entries, nineteen substances or groups of substances and three technological processes are listed as "known carcinogens":

4-Aminobiphenyl
Arsenic and certain arsenic compounds
Asbestos
Auramine manufacture
Benzene
Benzidine
N,N-Bis(2-chlorethyl)-2-naphthylamine (chlornaphazine)
Bis(chloromethyl)ether and technical grade chloromethyl methyl ether
Chlorambucil
Chromium and certain chromium compounds
Coke oven emissions
Cyclophosphamide
Diethylstilbestrol (DES)
Hematite underground mining
Isopropyl alcohol manufacture (strong-acid process)
Melphalan
Mustard gas
2-Naphthylamine
Nickel refining
Soots, tars, and mineral oils
Thorium dioxide
Vinyl chloride

Ninety-five 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 technological process, there is a summary description including a synopsis of the evidence that explains inclusion in this Report. This is followed by a collation of regulatory information received from the participating Agencies.

Among the 117 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.

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

There are 15 therapeutic substances: N, N-bis (2-chloroethyl) -2- naphthylamine; chlorambucil; cyclophosphamide; diethylstilbestrol; iron dextran complex; melphalan; oxymetholone; phenacetin; phenazopyridine hydrochloride; phenytoin; procarbazine; reserpine, selenium sulfide; streptozotocin; and tris(1-aziridinyl)phosphine sulfide. Two of these substances are no longer produced or used in the United States: N,N-bis(2-chloroethyl)-2-naphthylamine and streptozotocin. Six are anticancer agents: chlorambucil, cyclophosphamide, diethylstilbestrol, melphalan, procarbazine, and tris(1-aziridinyl)phosphine sulfide.

The remaining 83 substances may be classified as: various industrial chemicals and by-products (25); dye intermediates and pigments (19); combustion products (13); solvents (6); metals and metal compounds occurring in mining, extraction, and refining processes (6); analytical and research chemicals (5); and chemicals used for miscellaneous purposes (9).

The three occupational exposures known to be carcinogenic are those associated with the manufacture of auramine, underground hematite mining, and the manufacture of isopropyl alcohol by the strong-acid process.

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 sole 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. . . ."*

Corrections or suggestions, as well as any additional information that the reader may have, should be sent to: Director, National Toxicology Program, P.O. Box 12233, Research Triangle Park, North Carolina 27709.

*CDC/NIOSH, Consumer Product Safety Commission (CPSC), 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 Department of Labor/Occupational Safety and Health Administration (DOL/OSHA).

**Now part of NTP/NIEHS.

*So far only two substances have been banned on the basis of the "Delaney clause": Flectol H in 1967 and chloraniline in 1969. Both substances were used to make adhesives for food packaging material (FDA).

Copies of this Report summary 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 83-135855 should be indicated. Phone: (703) 487-4650.



## Introduction

Cancer is the second most common cause of death in the United States. One of every four Americans will suffer from cancer sometime during their lifetime; one in every five will die from cancer. In 1979, more than 400,000 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 $30 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 of 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 avertible, 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 workplace and in the general environment and how well we are protected from exposure to these substances.

Section 262 of Public Law 95-622 of November 9, 1978* 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 resid-

*Community Mental Health Centers Act. Amendments.

2. Reasonably anticipated to be carcinogens:
   A. There is "limited evidence of carcinogenicity" from studies of 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 of 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 this 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 can be associated with increased incidence of cancer in humans, but the substances responsible cannot be identified. Examples of such processes are the underground mining of hematite and the strong-acid process for the manufacture of isopropyl alcohol.

### 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 short-comings. 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, 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 almost all 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 that produce cancer in rodents and other experimental animals may affect human cells in the same way.

Relatively large doses of chemicals are used in animal studies to make up for the small number of experimental animals exposed, as compared to the size of human populations. Animal tests are costly, take years to complete, and are often difficult to interpret in terms of human carcinogenic risk. They are, nevertheless, the best testing tool we have. No animal test can 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 treated as if they may reasonably be anticipated to be human carcinogens.

*The evidence for carcinogenicity in experimental animals for arsenic is still regarded as inadequate and the evidence for benzene is at present limited.[6]

### Inclusion of Substances

The Third Annual Report contains substances, groups of substances, and technological processes which were listed in the Second Annual Report. Where necessary, the information has been updated. The Third Annual Report presents information on 28 additional substances. Each has been chosen either from substances tested by the NCI Carcinogenesis Testing Program or the NTP; from designations of the participating agencies; or from substances evaluated by the IARC working groups. Other substances from the same sources will be added to the subsequent Annual Reports.

The Table of Contents of the Third Annual Report lists all the substances and technological processes included. The list is divided into two sublists. One contains substances, groups of substances, or technological processes known to be carcinogens (22 entries). The other list of 95 entries includes substances or groups of substances which may reasonably be anticipated to be carcinogenic. 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 this 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 introduced as a result of testing performed by industry in response to EPA's requests under the Toxic Substances Control Act. The NTP will also play a role in providing 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 carcino

gens. They have not been included in this Report because ionizing radiation is discussed thoroughly in a General Accounting Office report, and a recent Surgeon General's report[8] reviews the overwhelming relationship between tobacco and cancer. Several publications issued by the National Cancer Institute explain the relationship of alcoholic beverages, ultraviolet radiation, and viruses to cancer.

### Estimating Exposure

According to clause (ii) of subparagraph (4)(A), this 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., safrole, 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 substance." The determination of the number of people 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. 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.

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 exposure, but this 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 exposed and on some broader aspects of occupational exposure. The forthcoming National Occupational Exposure Survey (a repeat of NOHS) should yield valuable information with respect to more recent 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 Third Annual Report responds to this 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, for instance, to prevent other adverse health effects or to improve the environmental quality or food quality. Solid or liquid wastes, or wastes discharged into the air may contain carcinogens, yet these may be regulated as toxic substances or hazardous pollutants and not specifically as carcinogens. But if these regulations reduce exposure to carcinogens, then the carcinogenic 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 carcinogenic 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 risk to public health. 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 likelihood 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-Healy Act which then regulated only the firms with Government contracts, the standard for permissible exposure was 12 fibers of asbestos per cubic centimeter (cc) of air. Under the Occupational Safety and Health Act, this standard was reduced to 5 fibers/cc in 1972 and to 2 fibers/cc 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. The high risk to 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 have reduced the cancer risk to those persons exposed to asbestos.

One possible way to provide quantitative estimates of risk reduction might be to assume that the carcinogenic 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]

## References


1. National Center for Health Statistics. Advance Report of Final Mortality Statistics, 1979, Monthly Vital Statistics Report 31, No. 6, Supplement, September 30, 1982.
2. Office of Technology Assessment, Congress of the United States. Assessment of Technologies for Determining Cancer Risks from the Environment. U.S. Government Printing Office, Washington, D.C., 1981, p. 3 and pp: 65–109.
3. Cole, P. Epidemiological Clues to Host Factors in Human Carcinogenesis. In: H. Bartsch and B. Armstrong (Eds.). Host Factors in Human Carcinogenesis. IARC Scientific Publications No. 39. International Agency for Research on Cancer, Lyon, 1982, p. 3.
4. Bartsch, H. and Armstrong, B. (Eds.). Host Factors in Human Carcinogenesis. IARC Scientific Publications No. 39. International Agency for Research on Cancer, Lyon, 1982, p. xi.
5. Griesemer, R.A., and Cueto, C., Toward a Classification Scheme for Degrees of Experimental Evidence for the Carcinogenicity of Chemicals for Animals. In: R. Montesano, H. Bartsch and L. Tomatis, (Eds.). Molecular and Cellular Aspects of Carcinogen Screening Tests, IARC Scientific Publications No. 27. International Agency for Research on Cancer, Lyon, 1980, pp. 259–81.
6. International Agency for Research on Cancer. Chemicals, Industrial Processes and Industries Associated with Cancer in Humans, IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. Supplement 4. IARC, Lyon, 1982.
7. Comptroller General, U.S. General Accounting Office. Problems of Assessing Cancer Risk of Low Level Ionizing Radiation Exposure. Report to the Congress of the United States, EMD-81-1, Washington, D.C., 1981.
8. Office of Smoking and Health. The Health Consequences of Smoking: Cancer, a Report of the Surgeon General, U.S. Department of Health and Human Services, Public Health Service, Rockville, Maryland, 1982.
9. See, for example, Shimkin, M.B. Science and Cancer, NIH Publications No. 80-568, Third Revision, National Cancer Institute, National Institutes of Health, U.S. Department of Health and Human Services, Bethesda, Maryland, 1980.

performed with rats were considered inadequate.[208,209]

There are case reports and epidemiological studies of lymphomas occurring in patients that received phenytoin; however, no excess of lymphomas was reported in a follow–up study of epilepsy patients, many of whom received phenytoin along with other anti–epileptic drugs. Three recent papers report one case of malignant mesenchymoma and two cases of neuroblastoma in children with phenytoin-induced malformations. An epidemiological study looked at the frequency of use of phenytoin and of phenobarbitone in mothers of children with childhood cancers compared with mothers of normal children. While more mothers of cancer cases reported a history of epilepsy, no differences were seen in the proportion of epileptic mothers who took either phenytoin or phenobarbitone. An excess of lymphomas was seen in children of epileptic mothers, but the occurrence of brain tumors was not reported.[208,209]

## Polybrominated biphenyls (PBBs)

Polybrominated biphenyls (PBBs) were widely used as flame retardant additives in synthetic fibers and in molded plastics. PBBs are solid at room temperature and practically insoluble in water. They are mixtures of compounds containing, on the average, six bromine atoms per molecule.

PBBs have been incorporated into the plastic housing of many commercial products. PBBs have been sold to manufacturers of polycarbonates, polyesters, polyolefins, and polystyrenes. The CPSC reported that hexabromobiphenyl (HBB) was the major component in the most widely used PBB mixture, and that PBBs are not presently being used in consumer products.

The commercial production of PBB began in 1970. Approximately 11 million lb of HBB were manufactured by a single U.S. company from 1970 to 1974 and marketed under the trade names Firemaster BP-6 and Firemaster FF-1. CPSC reported that the sole U.S. manufacturer of HBB ceased production in 1974. The remaining stock of this product held by the sole producer was reportedly exhausted in April 1975.

Other PBB production ceased in the late 1970s. EPA reported one U.S. producer (Toxic Substances Control Act (TSCA), Chemical Substance Inventory, 1979, public record). The U.S. production of other PBBs (decabromobiphenyl), as reported to the U.S. International Trade Commission, was greater than 10,000 lb for 1980, according to NCI.

Workers of a chemical company that manufactured PBB were directly exposed to PBB by skin contact, inhalation, and unintentional ingestion. HBB was detected in workers' sera at a range of 1.1 to 1729 ppb, and in their adipose tissue at a range of 0.51–581 ppm. Approximately 2000 lb of PBBs were inadvertently mixed into livestock feed in Michigan in 1973. Thousands of animals died or were destroyed. Initially, 8000 to 12,500 Michigan residents were exposed in 1973 and 1974 to meat, milk, and eggs contaminated with PBBs. A general population survey conducted in Michigan revealed that only 10 percent of the population did not have detectable levels of PBB in their blood. Because the PBBs are biologically stable and slowly eliminated, significant body burdens could persist throughout their lifetimes.

In 1974, the National Occupational Hazard Survey estimated that 4900 workers were potentially exposed to PBBs. The sources of PBBs currently appear to be residues remaining in and around plants that at one time manufactured, processed, or produced products using PBBs. FDA stated that a potential for human exposure exists from the ingestion of foods containing residues of these compounds.

EPA is currently proposing a reporting rule for PBBs under the TSCA, 8(a). Under section 406 of the Food, Drug, and Cosmetic (FD&C) Act, FDA regulates PBB compounds as unavoidable environmental contaminants. In cooperation with CDC and the Public Health Department of the State of Michigan, FDA monitors the long-term human health effects from acute exposure to PBBs.

Firemaster FF-1 (Firemaster BP-6 containing 2 percent of calcium trisilicate)—a mixture of pentabromobiphenyl, hexabromobiphenyl and heptabromobiphenyl with hexabromobiphenyl being the major component—administered by gavage produced neoplastic nodules and hepatocellular carcinomas in female Sherman strain rats.[210] In another bioassay, Firemaster FF-1—also administered by gavage—was carcinogenic to Fischer 344 rats and B6C3F1 mice of each sex, inducing neoplastic nodules, hepatocellular carcinomas, and cholangiocarcinomas in rats and hepatocellular carcinomas in mice.[211]

## Polychlorinated biphenyls (PCBs)

Polychlorinated biphenyls (PCBs) vary in appearance from mobile, oily liquids to white crystalline solids to hard noncrystalline resins, with all forms insoluble in water. 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 for copy paper. By 1974, all domestic uses of PCBs were confined to closed systems.

PCBs have been produced in the United States since 1929. Domestic production reached a peak volume of

[208]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 1. Lyon, France: IARC, 1979.

[209]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 13. Lyon, France: IARC, 1977, pp. 201–25.

[210]Kimbrough, R.D., D.F. Groce, M.P. Korver, and V.W. Burse. Induction of Liver Tumors in Female Sherman Strain Rats by Polybrominated Biphenyls. J. Nat. Cancer Inst. Vol. 66, No. 3, 1981, pp. 535–42.

[211]National Toxicology Program. Studies of Carcinogenesis Polybrominated Biphenyl Mixture (Firemaster FF-1). Technical Report Series No. 244. NIH Publication No. 83-1800. Research Triangle Park, North Carolina, 1983

86 million lb in 1970 and decreased to approximately 41 million lb by 1974. Annual domestic production prior to 1977 was approximately 35 million lb. Except for limited research and development applications, the PCBs are no longer produced in the United States, and no import or export of the compounds has been permitted since July, 1979.

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 exposure of the general public. Routes of exposure include skin absorption and ingestion; a major source of exposure is through the diet. A 1976 report indicated that fish, cheese, eggs, and contaminated animal feed were the 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 approximately 12 million persons within 12 miles of three existing and nine projected commercial incinerators could be exposed to releases of PCBs.

In 1970, EPA banned PCBs as a pesticide ingredient and canceled registration of products containing the PCBs. EPA promulgated toxic pollutant effluent standards in 1977 and modified the marking and disposal rule in 1979. This latter regulation has been effective in identifying and eliminating some sources. In 1979, EPA issued a ban on manufacturing, processing, and distributing of PCBs in commerce; most manufacturing had 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. Air pollution sources of PCBs were recently assessed by EPA, and the need for regulation of emissions from incinerators, the only source for which controls may be essential, is under consideration. Under the Safe Drinking Water Act, EPA is preparing a report to the Congress concerning 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 current tolerances 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 is currently considering the lowering of PCB standards 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 has adopted an 8-hour time-weighted average standard of 1 mg/m$^3$ for PCBs containing 42 percent chlorine, and 0.5 mg/m$^3$ for PCBs containing 54 percent chlorine. This standard was adopted by OSHA for toxic effects other than cancer.

The evidence for carcinogenicity of PCBs in experimental animals is sufficient, and the evidence in humans is inadequate.[212]

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.[213]

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.[212]

## Procarbazine and procarbazine hydrochloride

Procarbazine, an organic compound, is soluble but unstable in water or aqueous solutions.

Procarbazine hydrochloride is primarily used as an antineoplastic agent in the treatment of advanced Hodgkin's disease and oat-cell carcinoma of the lung. The FDA approved the use of procarbazine hydrochloride in 1969 and indicated that the drug should be used as an adjunct to standard therapy.

Possible exposure occurs during manufacture of the drug and direct exposure occurs during administration to patients. The National Prescription Audit reported 1.5 million prescriptions dispensed in 1980. Some of the metabolites of procarbazine are both carcinostatic and carcinogenic.

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.[214,215]

Laboratory exposure of animals to procarbazine was studied by intraperitoneal injection. In rats, malignant lymphoma, adenocarcinoma of the mammary gland, and olfactory neuroblastomas were induced in statistically significant numbers. In mice, malignant lymphoma or leukemia, olfactory neuroblastoma, alveolar/bronchiolar adenoma, and adenocarcinoma of the uterus were induced in statistically significant numbers.[215]

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

[212]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[213]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 18. Lyon, France: IARC, 1978, pp. 43–103.

[214]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 26. Lyon, France: IARC, 1981, pp. 311–39.

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

## Executive Summary

The Third 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 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 limited evidence of carcinogenicity in humans or sufficient evidence of carcinogenicity in experimental animals.

Substances in the above categories for which 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 fact that a substance is not contained in the Third Annual Report does not mean that it is not a known or reasonably-anticipated carcinogen.

Several problems are encountered in developing the information required for the Annual Reports on Carcinogens. Estimating the number of people exposed to a substance and identifying the nature, route, and intensity of 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 exposure estimates in the future. In addition, the forthcoming National Occupational Exposure Survey* will provide new information on the extent and degree of exposure for different substances and manufacturing processes.

Perhaps the hardest task in preparing this Report is to evaluate the effectiveness of Federal regulations in decreasing the risk to public health. One reason is that virtually all Federal laws concerned with reducing risk have been enacted within the last 15 years

*An update of the National Occupational Hazard Survey conducted from 1972 to 1974 by the [illegible]