9th Report on Carcinogens

2000



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Public Health Service
National Toxicology Program
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INTRODUCTION

The probability that a resident of the United States will develop cancer at some point in his or her lifetime is 1 in 2 for men and 1 in 3 for women (ACS, 1999). Nearly everyone's life has been directly or indirectly affected by cancer. Most scientists involved in cancer research believe that a significant fraction of all cancer cases may be associated with the environment in which we live and work. In this context, the "environment" is defined as anything that interacts with humans, including lifestyle choices, such as substances eaten, drunk, and smoked, and aspects of sexual behavior; natural and medical radiation, including exposure to the sun; workplace exposures; drugs; socioeconomic factors affecting exposures and susceptibility; and substances in air, water, and soil (OTA, 1981). Other factors that play a major role in cancer development are aging and individual susceptibility, such as genetic predisposition. We rarely know what environmental factors and conditions are responsible for the onset and development of cancers. However, in some cases, we have some understanding, especially for cancers related to certain occupational exposures or the use of specific drugs or cancer chemotherapeutic agents. Many scientists knowledgeable in these areas firmly believe that much of the cancer associated with the environment may be avoided (Tomatis et al., 1997).

The people of the United States, concerned about the relationships between their environment and cancer, have asked, through the U.S. Congress, for information about substances that are known or appear likely to cause cancer. Section 301 (b) (4) of the Public Health Service Act, as amended[1], provides that the Secretary of the Department of Health and Human Services (DHHS) shall publish a biennial report that contains the following information:

(A) A list of all substances (1) which either are known to be human carcinogens or may reasonably be anticipated to be human carcinogens and (2) to which a significant number of persons residing in the United States are exposed.

(B) Information concerning the nature of such exposure and the estimated number of persons exposed to such substances.

(C) A statement identifying (1) each substance contained in this list for which no effluent, ambient, or exposure standard has been established by a Federal agency and (2) for each effluent, ambient, or exposure standard established by a Federal agency with respect to a substance contained in this list, the extent to which such standard decreases the risk to public health from exposure to the substance.

(D) A description of (1) each request received during the year to conduct research into, or testing for, the carcinogenicity of a substance and (2) how the Secretary and other responsible entities responded to each request.

The Report on Carcinogens is an informational scientific and public health document that identifies and discusses agents, substances, mixtures, or exposure circumstances that may pose a carcinogenic hazard to human health. It serves as a meaningful and useful compilation of data on the (1) carcinogenicity, genotoxicity, and biologic mechanisms of the listed substances in humans and/or animals, (2) the potential for exposure to these substances, and (3) the regulations promulgated by Federal agencies to limit exposures. The Report does not present quantitative

[1] "Section 262 of Public Law 95-622, the Community Mental Health Extension Centers Act of 1978, enacted November 9, 1978, added section 301(b)(4) but provided for annual reports. In 1993, the provision was amended to provide for biennial reports. "

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assessments of carcinogenic risk. Listing of substances in the Report, therefore, does not establish that such substances present carcinogenic risks to individuals in their daily lives. Such formal risk assessments are the purview of the appropriate Federal, State, and local health regulatory and research agencies.

Potential Beneficial Effects of Listed Carcinogens

As stated above, the Report on Carcinogens is a cancer health hazard identification document. Therefore it is not within the scope of this report to address potential benefits of exposures to certain carcinogenic substances in special situations. For example, numerous pharmaceuticals used in typical cancer chemotherapeutic or other medical treatment programs have been shown to increase the frequency of primary or secondary cancers in patients undergoing treatment for specific diseases. In these instances, the benefits of exposure to the drug for treatment or prevention of a specific disease outweigh the additional carcinogenic risks associated with its use. Personal decisions concerning voluntary exposures to carcinogenic agents should be based on information that is beyond the scope of this Report. Individuals should not make decisions concerning the use of a given drug, or any other listed agent, based on the information contained in this report. Decisions of this type should only be made after consulting with a physician or other appropriate specialist.

Identification of Carcinogens

For many years, government research agencies (including the National Toxicology Program), industries, academia, and other research organizations have studied various substances to identify those that might cause cancer. Most of this information on specific chemicals or occupational exposures has been published in the scientific literature or in publicly available and peer-reviewed technical reports; this literature is a primary source of information for identifying and evaluating substances for listing in these Reports. Many of the agents, substances, mixtures, and exposure circumstances listed in the Report on Carcinogens also have been reviewed and evaluated by other organizations, including the International Agency for Research on Cancer (IARC), in Lyon, France, the Environmental Protection Agency of the State of California, and other U.S. Federal and international agencies.

Both human and animal studies are used to evaluate whether chemicals are possible human carcinogens. The strongest evidence for establishing a relationship between exposure to any given chemical and cancer in humans comes from epidemiological studies. These studies of human exposure and cancer must consider the latency period for cancer development, because the exposure to the carcinogen often occurs many years (sometimes 20 to 30 years or more) before the first sign of cancer appears. However, the most common method for identifying substances as potential human carcinogens is the long-term animal bioassay. These bioassays provide accurate information about dose and duration of exposure and interactions of the substance with other chemicals or modifiers. In these studies, the chemical, substance, or mixture is administered to one or, usually, two laboratory rodent species over a range of doses and duration of exposure with all experimental conditions carefully chosen to maximize the likelihood of identifying any carcinogenic effects (Huff, 1999).

It is not possible to predict with complete certainty from animal studies alone which agents, substances, mixtures, or exposure circumstances will be carcinogenic in humans. However, all known human carcinogens that have been tested adequately also produce cancers in laboratory animals. In many cases, an agent was found to cause cancer in animals and only

subsequently confirmed to cause cancer in humans (Huff, 1993). Experimental carcinogenesis research is based on the scientific assumption that chemicals causing cancer in animals will have similar effects in humans. Laboratory animals' adverse responses to chemicals (of which cancer is only one) do not always strictly correspond to human responses; however, laboratory animals remain the best tool for detecting potential human health hazards of all kinds, including cancer (OTA, 1981; Tomatis et al., 1997).

Listing Criteria

For the first seven Annual Reports on Carcinogens, the following criteria were used for listing an agent, substance, mixture, or exposure circumstance:

***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.

***Reasonably Anticipated To Be a Human Carcinogen*:**

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.

During 1994 and 1995, the criteria for listing an agent, substance, mixture, or exposure circumstance in the Report on Carcinogens and for delisting a substance were revisited in a series of open public meetings. In recognition of advances in understanding the biological events involved in carcinogenesis, the criteria for listing were expanded to include a broader array of information related to the carcinogenic processes. In addition to epidemiology studies and studies to detect carcinogenic effects in experimental animals, other information contributing to scientific judgments about carcinogenicity was formally introduced into the process of deciding whether to list a chemical. Also, formal procedures for consideration of nominations to remove an agent, substance, mixture, or exposure circumstance from the listings were adopted (see Section V for details of listing and delisting procedures).

The revised criteria for listing an agent, substance, mixture, or exposure circumstance in the Report on Carcinogens were approved by the Secretary, DHHS, on September 13, 1996. The agents, substances, mixtures, or exposure circumstances newly included in or removed from the Eighth and Ninth Reports on Carcinogens were evaluated according to the following revised criteria:

***KNOWN TO BE HUMAN CARCINOGEN*:**

There is sufficient evidence of carcinogenicity from studies in humans which indicates a causal relationship between exposure to the agent, substance, or mixture and human cancer.

REASONABLY ANTICIPATED TO BE HUMAN CARCINOGEN:

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 factors, could not adequately be excluded, or

there is sufficient evidence of carcinogenicity from studies in experimental animals which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors (1) in multiple species or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site, or type of tumor or age at onset, or

there is less than sufficient evidence of carcinogenicity in humans or laboratory animals; however, the agent, substance or mixture belongs to a well-defined, structurally related class of substances whose members are listed in a previous Report on Carcinogens as either known to be a human carcinogen or reasonably anticipated to be a human carcinogen, or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to, dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub-populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans.

Preparation of Reports on Carcinogens

Within the Department of Health and Human Services, the Secretary has delegated the responsibility for preparing these Reports to the National Toxicology Program (NTP). The process used to prepare the Reports on Carcinogens involves several levels of review, both of the substances, agents, mixtures, and exposure circumstances considered for listing in or delisting from the Reports and of the draft Reports prior to publication. Continuing opportunities for public comment and participation are an integral part of the process.

Nominations for listing in or delisting from the RoC are received from a number of sources. Periodic requests for nominations from the public are published in the Federal Register, the NTP Liaison Office Update, and other appropriate publications. The NTP actively solicits nominations from member agencies of the NTP Executive Committee[2]. Nominations for the

[2] Agencies represented on the NTP Executive Committee include:

RoC also come from reviews of the literature performed by the NTP. Potential nominations are identified from such sources as the NTP Bioassay Technical Reports, the IARC Monographs, the State of California Environmental Protection Agency Carcinogen List, and other similar sources.

Two Federal scientific review groups and one nongovernmental scientific peer-review body (a subcommittee of the NTP Board of Scientific Counselors) evaluate the nominations for listing in or delisting from the Reports on Carcinogens. Each group reviews data on the carcinogenicity of the substances and on exposure of U.S. residents to the substances. The membership of these three review groups may be found in Appendix D, List of Participants.

The first Federal scientific review group is the NIEHS/NTP Report on Carcinogens Review Committee (RG1), composed of scientists from the NIEHS/NTP. Nomination of an agent, substance, mixture or exposure circumstance for listing or delisting is announced in the Federal Register, NTP newsletters and web pages and other appropriate publications to solicit public comment. The original nomination and all public comments received are evaluated by the RG1 to determine whether the information provided is sufficient to warrant further consideration of the nomination.

If the RG1 determines that the nomination warrants formal consideration, the NTP may initiate an independent search of the literature and prepare a draft background document for the substance under consideration. The RG1 places emphasis on the carcinogenicity and related toxicological exposure and other data and on issues identified in the public comments, submitted concerning the nomination and also reviews information on exposure provided in the study reports and monographs. Following the reviews the RG1 makes a formal recommendation to the Director, NTP, for listing or delisting in the Report on Carcinogens.

If the RG1 determines that a nomination contains insufficient information to warrant consideration by the NTP, the nomination is returned to the original nominator, who is invited to resubmit the nomination with additional justification, such as new experimental data or exposure information, etc. If the RG1 finds insufficient justification for consideration of a nominated substance notice stating the action taken is published in the Federal Register, trade journals, and NTP publications and is included in subsequent editions of the Report, with the reason(s) why the substance was not considered further. The decision also is forwarded to the NTP Board of Scientific Counselors and the NTP Executive Committee.

The second Federal scientific review group is the NTP Executive Committee Interagency Working Group for the Report on Carcinogens (RG2). The RG2 is a governmental interagency group that provides a second, independent assessment of whether the information available for the nominated agent, substance, mixture, or exposure circumstance warrants its listing in or delisting from the RoC. Upon completion of its review, the RG2 makes a recommendation to the Director, NTP, for listing or delisting in the RoC.

External peer review of the nominations is performed by a subcommittee of the NTP Board of Scientific Counselors. The subcommittee reviews nominations in open, public meetings. Prior to public review, a notice is published in the Federal Register, NTP newsletters and web pages and other appropriate publications, again soliciting public comment. The notice

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Agency for Toxic Substances and Disease Registry (ATSDR), Consumer Product Safety Commission (CPSC), Environmental Protection Agency (EPA), Food and Drug Administration (FDA), National Center for Toxicological Research (NCTR), National Institute for Occupational Safety and Health (NIOSH), Occupational Safety and Health Administration (OSHA), Department of Health and Human Services (DHHS), National Institutes of Health (NIH), National Cancer Institute (NCI), and National Institute of Environmental Health Sciences/NTP (NIEHS/NTP)

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also invites interested groups or individuals to submit written comments or to address the subcommittee during the review meeting. Upon completion of its review, the subcommittee provides its recommendations to the Director, NTP, for listing or delisting in the Report.

Following the Board Subcommittee review, an announcement is published in the Federal Register, NTP newsletters and web pages and other appropriate publications that contains the recommendations of the three (3) scientific review groups, and solicits final public comment and input for nominations. The recommendations of the three scientific review groups and all public comments, are provided to the NTP Executive Committee, who review this information and provide the Director, NTP their recommendations. All recommendations and public comments are then reviewed by the Director, NTP, who forwards the final draft of the Report that contains his recommendations to the Secretary, DHHS for the listings or delistings in the Report on Carcinogen. Upon review and approval by the Secretary, DHHS, and submission to Congress, a notice of the Report on Carcinogens publication, indicating all newly listed or delisted agents, substances, mixtures or exposure circumstances is published in the Federal Register, NTP newsletters and web pages and other appropriate publications.

Estimation of Exposure

This Report is required to list only substances to which a significant number of people residing in the United States are exposed. For the most part substances to which very few people are exposed are not listed. Some substances that have been banned or restricted in use are listed (e.g., safrole, arsenical pesticides, and mirex), either because people who were previously exposed remain potentially at risk or because these substances still are present in the environment.

This Report also is required to provide information concerning the nature of exposure and the estimated number of persons exposed to listed substances. Four of the agencies participating with the NTP in the preparation of the Ninth Report - the Consumer Product Safety Commission (CPSC), U.S. Environmental Protection Agency (EPA), Food and Drug Administration (FDA), and Occupational Safety and Health Administration (OSHA) - are responsible for regulating hazardous substances and limiting the exposure to and use of such substances. Information in each entry of the Report on Carcinogens on Use, Production, and Exposure is provided by participants from these regulatory agencies. Determination of the number of people potentially exposed and the route, intensity, and duration of exposure for each substance remains a formidable task. This Report attempts to respond to these questions; wherever adequate answers could be obtained, they are included in Sections III-A and III-B.

The National Occupational Hazard Survey (NOHS), conducted by the National Institute for Occupational Safety and Health (NIOSH) from 1972 to 1974, and the National Occupational Exposure Survey (NOES) (1981 to 1983) have yielded potential exposure data for many listed substances. Although dated, NOES estimates are provided in the profiles of the substances where available, NOHS figures are given in some profiles where no other data are available.

Regulatory Status

To meet the requirement to identify each listed substance for which no effluent, ambient, or exposure standard has been established by a Federal agency, the Ninth Report appends to the description of each substance a summary of Federal regulations promulgated by the participating

agencies[3]. 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 quality of the environment or food. 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. If these regulations reduce exposure to carcinogens, then the cancer risk posed by such substances will likely decrease.

The regulations tables and text of the substance profiles in the Eighth Report on Carcinogens have been updated in the Ninth Report on Carcinogens.

Estimation of Risk Reduction

For each effluent, ambient, or exposure standard established by a Federal agency with respect to a listed substance, this Report is required to state the extent to which, on the basis of available medical, scientific, or other data, the implementation of such standard decreases the risk to public health from exposure to the substance. This requires quantified information on the extent of protection from cancer that the public receives from established Federal standards.

Estimating the extent of health protection is perhaps the most difficult task in preparing the Report. One reason is that most Federal laws concerned with reducing cancer risk have been enacted only within the last 15 to 20 years. Given the typically long period between the initial exposure to a carcinogen and the onset of disease, it is still too early to evaluate to what extent 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 is inaccurate.

The risk-the probability of developing cancer-depends on many things, including the intensity, route, and duration of exposure to a carcinogen or carcinogens. 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 complete confidence.

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 (Tomatis et al., 1997). This is the basis of current regulatory policies that aim to lower human exposure to cancer-causing substances and thereby improve public health.

[3] Throughout these volumes, NIOSH recommendations are included in the tables of regulations. Although NIOSH is not a regulatory agency, the NIOSH findings often are used in formulation of regulatory actions.

Listing, Upgrading, and Delisting of Substances in the Ninth Report

The Ninth Report on Carcinogens contains 218 entries, 14 of which have not appeared in earlier Reports. This Report also reclassifies 1,3-butadiene, cadmium and cadmium compounds, Direct Black 38, Direct Blue 6, ethylene oxide, and silica (crystalline, respirable size) from *reasonably anticipated to be a human carcinogen* to *known to be a human carcinogen*, with corresponding revisions of the earlier entries for these chemicals. Two substances, saccharin and ethyl acrylate, have been removed from the Ninth Report on Carcinogens as a result of formal reviews for delisting. Profiles that contain the relevant information and the issues that led to these substances' removal from the Report on Carcinogens are included in Appendix B of this Report.

Scientific reviews also were conducted for the following substances or exposure circumstances nominated for listing or upgrading in the Ninth Report:

•Employment in the boot and shoe manufacture and repair industry as an occupational exposure circumstance was reviewed for listing in the Ninth Report. Following an initial review by the three Report on Carcinogens scientific review groups, it was recommended that further action on this nomination be deferred until guidelines to define the issues that need to be addressed when reviewing worker exposure circumstances for listing in the Report on Carcinogens have been established. Therefore boot and shoe manufacture and repair remain in Appendix A of the Ninth Report, which lists manufacturing processes, occupations, and exposure circumstances classified by IARC as carcinogenic to humans.

•Methyl-tertiary-butyl ether (MtBE) was not recommended for listing in the Ninth Report, following a formal scientific review. The basis for the recommendation not to list MtBE is summarized in a table in Appendix C of this Report.

•Nickel and certain nickel compounds were listed in the Eighth Report as *reasonably anticipated to be human carcinogens*. Nickel compounds were reviewed for possible listing in the Ninth Report on Carcinogens. Metallic nickel and nickel alloys will be reviewed for possible listing in the Tenth Report. The new listing of Nickel compounds will be deferred until the completion of the review of metallic nickel and nickel alloys. Nickel and certain nickel compounds will remain listed in Ninth Report as *reasonably anticipated to be human carcinogens*.

•2,3,7,8-Tetrachlorodibenzo-*p*-dioxin has been proposed for upgrade to the *known to be a human carcinogen* category. The proposed listing is currently in litigation. Depending on the outcome of the litigation an addendum may be published following the Court's ruling.

Section II of this Report contains the names and synonyms of all the agents, substances, mixtures, or exposure circumstances listed in the Ninth Report as either *known to be human carcinogens* (section II. 1), or as *reasonably anticipated to be human carcinogens* (Section II. 2).

Section III, Carcinogen Profiles, contains a brief description of each agent, substance, mixture, or exposure circumstance, with a summary of evidence for its carcinogenicity. The profiles are divided into two categories. The first category, III-A, lists 47 agents, substances, mixtures, or exposure circumstances *known to be human carcinogens*. The second category, III-B, lists 171 agents, substances, mixtures, or exposure circumstances *reasonably anticipated to be human carcinogens*. References to the original papers on experimental and epidemiological

studies can be found in the supporting background documents, the IARC Monographs, or the National Cancer Institute (NCI) and NTP bioassay reports.

The agents, substances, mixtures or exposure circumstances listed in the Ninth Report may constitute only a fraction of actual known or reasonably anticipated human carcinogens. The substances listed in the Report are those for which relevant data exist and have been reviewed and found to meet the criteria for listing. As additional substances are nominated, they will be considered and reviewed for possible listing in future Reports.

Certain manufacturing processes, occupations, and exposure circumstances have been considered by IARC and classified by the agency as known to be carcinogenic to humans because of associated increased incidences of cancer among workers in these settings. The NTP has not yet reviewed the data supporting the listing of these occupational situations as posing a carcinogenic hazard to humans. Certain aspects of occupational exposures may differ in different parts of the world or may have changed over time; therefore, the manufacturing processes and occupations reviewed by IARC may not be applicable to past or current occupational exposures in the United States. In the interest of public health and for completeness, these occupational exposures are found in Appendix A of this Report, with the corresponding IARC references.

Other Information Provided in this Report

Section IV of this report provides tables listing request to DHHS for research, testing, and other information relating to carcinogenicity, either from other federal agencies or from within DHHS, along with how requests were responded to. Section V gives listing and delisting procedures for the Report on Carcinogens. Section VI of this Report, which is published as a separate Volume (II), contains a cumulative list of Code of Federal Regulations and Federal Register citations for each listing in the Ninth Report.

The Ninth Report also includes eight appendices. Appendix A is a list of manufacturing processes, occupations, and exposure circumstances classified by IARC as known to be carcinogenic to humans. Appendix B is a list of Agents, Substances, Mixtures, or Exposure Circumstances Removed from the Report on Carcinogens. Appendix C is a list of Agents, Substances, Mixtures, or Exposure Circumstances Reviewed but Not Recommended for Listing in the Report on Carcinogens. Appendix D is a list of participants who collaborated in preparing the Ninth Report. Appendices E, F, and G are, respectively, a glossary of terms, a list of acronyms and abbreviations, and a list of units of measurement used frequently in the Ninth Report. Appendix H is a list of Chemical Abstracts Service Registry Numbers (CASRNs) of chemical substances listed in this Report. The CASRN index indicates the page number where a profile of the substance appears in the Ninth Report and the year the substance was first listed in an NTP Report on Carcinogens.

Unlike earlier editions of the Report on Carcinogens that were published as both full and summary reports, the Ninth Edition of the Report on Carcinogens is published as a single Report.

For more information on the Ninth Report on Carcinogens, including how to order a hard copy of the Report or access it on the Web, visit the NTP Report on Carcinogens Homepage at http://ntp-server.niehs.nih.gov/NewHomeRoc/AboutRoC.html or by contacting the National Toxicology Program, Report on Carcinogens, MD EC-14, P.O. Box 12233, Research Triangle Park, NC 27709. For information, contact Dr. C. W. Jameson, telephone: (919) 541-4096, fax, (919) 541-0144, e-mail, jameson@niehs.nih.gov.

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ASBESTOS
CAS No. 1332-21-4
First Listed in the *First Annual Report on Carcinogens*

CARCINOGENICITY

Asbestos and all commercial forms of asbestos are *known to be human carcinogens* based on sufficient evidence of carcinogenicity in humans (IARC S.4, 1982). Occupational exposure to chrysotile, amosite, anthophyllite, and mixtures containing crocidolite has resulted in a high incidence of lung carcinomas. Mesotheliomas have been observed after occupational exposure to crocidolite, amosite, and chrysotile asbestos. Gastrointestinal cancers occurred at an increased incidence in groups occupationally exposed to crocidolite, amosite, chrysotile or mixed fibers containing crocidolite, although not all studies are consistent in this respect. An excess of laryngeal cancer has also been observed in some groups of exposed workers. No clear excess of cancer has been associated with the presence of asbestos fibers in drinking water. Mesotheliomas have occurred in individuals living in the neighborhood of asbestos factories and mines and in people living with asbestos workers (IARC S.7, 1987). Both cigarette smoking and occupational exposure to asbestos fibers increase lung cancer incidence independently. When present together, they act multiplicatively (IARC V.2, 1973; IARC V.14, 1977; IARC S.1, 1979; IARC S.4, 1982). A study based upon findings from two asbestos cement manufacturing plants has shown evidence of a greater risk of mesothelioma from exposure to crocidolite than to chrysotile asbestos (Hughes et al., 1987).

An IARC Working Group reported that there is sufficient evidence of carcinogenicity of asbestos and the following forms of commercial asbestos: chrysotile (12001-29-5), amosite (12172-73-5), anthophyllite (17068-78-9), and crocidolite (12001-28-4) in experimental animals: (IARC V.2, 1973; IARC V.14, 1977; IARC S.1, 1979; IARC S.4, 1982; IARC S.7, 1987). When administered by inhalation, chrysotile, crocidolite, amosite, and anthophyllite induced mesotheliomas and lung carcinomas in rats and mesotheliomas after intrapleural administration. Chrysotile, crocidolite, amosite, and anthophyllite induced mesotheliomas in hamsters after intrapleural administration. Intraperitoneal administration of chrysotile, crocidolite, and amosite induced peritoneal tumors, including mesotheliomas, in mice and rats. Given by the same route, crocidolite induced abdominal tumors in hamsters, and actinolite induced abdominal tumors in rats. When filter material containing chrysotile was added to the diet, a statistically significant increase in the incidence of malignant tumors was observed in rats. Tumor incidence was not increased by oral administration of amosite in rats, of amosite in hamsters, or of chrysotile in hamsters. There was no evidence of carcinogenicity for pelleted short-range (SR) chrysotile (for rats of both sexes) or for pelleted intermediate-range (IR) fiber length chrysotile for female rats when added to the diet for the lifespan. In the same study, there was a low incidence of benign adenomatous polyps of the large intestine in male rats administered IR chrysotile (NTP 295, 1985). Cocarcinogenesis studies of 1,2-dimethylhydrazine dihydrochloride (DMH) and IR chrysotile were inconclusive for determining whether IR chrysotile had a tumor-enhancing effect, although an increased incidence of neoplasms was observed in the kidneys of female rats exposed to DMH plus IR chrysotile as compared with those exposed to DMH alone (NTP 295, 1985).

PROPERTIES

Asbestos is the generic name given to a class of natural fibrous silicates that vary considerably in their physical and chemical properties. Chrysotile has an idealized chemical composition of $Mg_3(Si_2O_5)(OH)_4$. The composition of chrysotile is typically as follows: SiO_2, 37%-44%; MgO, 39%-44%; FeO, 0%-6.0%; Fe_2O_3, 0.1%-5.0%; Al_2O_3, 0.2%-1.5%; CaO, trace to 5.0%; H_2O, 12.0%-15.0%. Common minerals found in commercial grades include magnetite, chromite, brucite, calcite, dolomite, and awaruite. Chrysotile's crystal structure is fibrous and asbestiform. It is white, gray, green, or yellowish, with a silky luster. It is soluble in acid. Amosite has a typical chemical composition of the following: SiO_2, 49%-53%; MgO, 1%-7%; FeO, 34%-44%; K_2O, 0%-0.4%; Na_2O, trace; and H_2O, 2.5%-4.5%. Amosite has a prismatic, lamellar to fibrous crystal structure. It is ash gray, greenish, or brown with a vitreous, somewhat pearly luster. It is fairly resistant to acids. Anthophyllite's typical chemical composition is as follows: SiO_2, 56%-58%; MgO, 28%-34%; FeO, 3%-12%; Al_2O_3, 0.5%-1.5%; and H_2O, 1%-6%. It has a prismatic, lamellar to fibrous crystal structure. Anthophyllite is gray-white, brown, gray, or green in color, with a vitreous to pearly luster. It is fairly resistant to acids. Crocidolite has the following chemical composition: SiO_2, 49%-53%; MgO, 0%-3%, FeO, 13%-20%; Fe_2O_3, 17%-20%; Al_2O_3, 0%-0.2%; CaO, 0.3%-2.7%; K_2O, 0%-0.4%; Na_2O, 4%-8.5%; and H_2O, 2.5%-4.5%. Crocidolite has a fibrous crystal structure. It is lavender or blue, with a silky dull luster. Crocidolite is fairly resistant to acids.

USE

Domestically used asbestos fibers are technically classified into seven quality categories or grades. Grades 1, 2, and 3 include the longer, maximum-strength fibers and are generally used in the production of textiles, electrical insulation, and pharmaceutical and beverage filters. Grades 4, 5, and 6 are medium-length fibers used in the production of asbestos-cement (A/C) pipe, A/C sheet, clutch facings, brake linings, asbestos paper, packaging, gaskets, and pipe coverings. Grade 7 includes short fibers generally used as a reinforcer in plastics, floor tiles, coatings and compounds, some papers, and roofing felts (OSHA, 1986).

The four commercially important forms of asbestos are chrysotile, amosite, anthophyllite, and crocidolite. Asbestos was consumed in roofing products, 34%, friction products, 23%, asbestos-cement, 15%, and gaskets, 8%; and other items, 20% (USDOI, 1991). Chrysotile is the most abundant form of asbestos; as such, it is the most commercially important form (IARC V.2, 1973). Chrysotile, amosite, and particularly crocidolite all have extremely high-tensile strengths and are used extensively as reinforcers in cements, resins, and plastics. Chrysotile fibers are soft and flexible, whereas crocidolite and amosite fibers are hard and brittle. Although chrysotile is most adaptable to industrial use, crocidolite and amosite are particularly useful in combination with chrysotile for adding specific properties, such as rigidity (OSHA, 1986). Due to its flexibility and softness, chrysotile can be more readily spun into textiles than the amphiboles (amosite, anthophyllite, and crocidolite) (Kirk-Othmer V.3, 1978). Asbestos has been used in more than 5,000 products, including roofing, thermal and electrical insulation, cement pipe and sheet, flooring, gaskets, friction materials, coatings, plastics, textiles, and paper products. Major research, however, is currently underway to develop and determine suitable substitutes for asbestos. Materials that have been found to serve as asbestos substitutes are the following: polypropylene and glass for reinforcement of cement; mineral wool for insulation board; ceramic paper for dental castings; alumina and zirconia for high temperature insulation and filtration; and glass, carbon, steel, vermiculite, and silicon nitride for friction materials (HSDB, 1997).

PRODUCTION

The production volume of asbestos in the United States has decreased significantly from the high output of nearly 300 million lb in the late 1960s and early 1970s to an estimated all-time low of 33.1 million lb in 1993. The majority of asbestos used in the United States is imported mainly from Canada (98%). The amounts imported, however, declined from 721 million lb in 1980 to 73 million lb in 1993 (ATSDR, 1995-K005). The asbestos industry per se had its inception in the 18th century, and by the mid-19th century both chrysotile and tremolite were mined and processed into commercial products (Kirk-Othmer V.3, 1978).

EXPOSURE

The primary routes of potential human exposure to asbestos are dermal contact, inhalation, and ingestion. Asbestos is used so widely that the entire population is potentially exposed to some degree. The number of workers exposed to asbestos since 1950 has greatly increased, but the intensity of occupational exposure has decreased (McDonald, 1985). Gross pollution in the areas of mines, factories, and shipyards is far less than 30 to 50 years ago, but general levels of exposure to the fibers in air, water, and food has increased from building construction and demolition and the deterioration and wearing of asbestos-containing materials. Worker exposure is a concern in the mining and milling of asbestos, during the manufacture of all asbestos products, and in the construction and shipbuilding industries. OSHA reported that about 2.5 million workers are estimated to have some potential exposure to asbestos. In addition, worker exposure occurs in asbestos end-product use occupations, e.g., asbestos insulation workers, brake repair and maintenance workers, building demolition workers, and asbestos abatement workers. The National Occupational Exposure Survey (NOES) (1981-1983) estimated that 153,937 total workers, including 7,603 women, were potentially exposed to asbestos (NIOSH, 1984). The total estimate was based on actual observations of asbestos (41%) and its use in tradename products (59%). The NOES estimated that 30,594 total workers, including 3,410 women, potentially were exposed to chrysotile. The total estimate was based on observations of actual use of chrysotile (12%) and its use in tradename products (88%). Asbestos concentrations in industrial air vary from 10 to 100,000 ng/m^3, depending upon the type of occupational exposure (IARC V.14, 1977). The ACGIH has established threshold limit values as 8-hr time-weighted averages (TWAs) of 0.5 fiber/cm^3 for amosite, 2 fibers/cm^3 for chrysotile, 0.2 fiber/cm^3 for crocidolite, and 2 fibers/cm^3 for other forms of asbestos (ACGIH, 1996).

People may encounter higher-than-average environmental asbestos concentrations in air if they live near an asbestos-containing waste site or asbestos-related industry, if they use any of a variety of asbestos-containing products, if they live or work in a building with deteriorating asbestos insulation, or if they live or work in a building that has undergone a poorly performed asbestos removal operation (ATSDR, 1995-K005). Families of asbestos workers were potentially exposed to high fiber levels through contaminated clothing brought home for laundering. Asbestos exposure levels ranging from 100 to 500 ng/m^3 were detected in houses of workmen (IARC V.14, 1977). Household contacts of asbestos workers were found to have significantly elevated pulmonary asbestos burdens, often in the range of those individuals who are occupationally exposed to asbestos, such as shipyard workers; the asbestos body (AB) count for the contacts ranged from 2 to 8200 AB/g, while the normal range, as determined in persons with no evidence of asbestos exposure or an asbestos-related disease, was 0 to 20 AB/g. The fiber burdens of occupants of a building containing asbestos insulation, on the other hand, were comparable to those of individuals with no known occupational exposure to asbestos; the range of the former was < 0.2 to 14 AB/g (Roggli and Longo, 1991). Dermal absorption of asbestos is

minimal, but contact may lead to secondary ingestion. Exposure in dental filling materials is assumed to be very low to practically nonexistent (IARC V.14, 1977).

Asbestos fibers are released into the environment from the natural occurrence of asbestos in the earth and as a result of wear and deterioration of asbestos products. Asbestos minerals are emitted into the water systems and atmosphere from the mining and milling of asbestos ores. Average concentrations of asbestos in drinking water ranged from 0.3 to 1.5 µg/L as measured in eastern U.S. river water. Concentrations not exceeding 100 ng/m^3, and usually less than 10 ng/m^3, of asbestos fibers are present in the general urban atmosphere (IARC V.14, 1977). Out in the country, away from anthropogenic or natural sources of asbestos, it is estimated that the ambient air concentration of asbestos is < 0.01 ng/m^3 (Chem. Eng. News, 1985a). Applications of asbestos materials to buildings and vehicle brake linings account for a significant amount of emissions to the atmosphere. Demolition of buildings with asbestos insulation or fireproofing may cause high atmospheric concentrations for relatively short periods of time. Disposal of mining and building material wastes in landfills also increases the distribution of asbestos into the environment, but no estimates of the quantity of material released in this manner are available. The Toxic Chemical Release Inventory (EPA) listed 131 industrial facilities that produced, processed, or otherwise used asbestos in 1988 (TRI, 1990). In compliance with the Community Right-to-Know Program, the facilities reported releases of asbestos to the environment which were estimated to total 1.2 million lb. More recently, the TRI has estimated a total of 235,000 lb of asbestos discharged to land (95.3% of the total environmental release), 11,264 lb discharged to the air (4.5%), and 250 lb discharged to surface water (< 1%) from manufacturing and processing facilities in the country in 1992 (ATSDR, 1995-K005).

REGULATIONS

CPSC's banning of asbestos in patching compounds and in gas fireplaces prevented additional possible exposure of several million consumers who may have been exposed to asbestos from these sources. U.S. manufacturers of hand-held hair dryers cooperated with CPSC by voluntarily ceasing to use asbestos liners; this voluntary program resulted in the repair by manufacturers of 2 million dryers. Also, CPSC published an intent to further regulate the uses of asbestos, and convened a Chronic Hazard Advisory Panel to assess and, if feasible, to estimate the probable harm to human health that can result from exposure to asbestos. The panel met for the first time in January 1983 and presented a draft report. Public comment was requested, and the final report was published in July 1983. Studies on the release of asbestos from products were completed in FY 1984. Toxicity reviews of major selected asbestos substitutes occurred in FY 1986. CPSC monitored air levels of asbestos in 45 homes, using transmission electron microscopy. The study concentrated on homes with quantities of worn and damaged asbestos materials. The results of this limited study did not show increased indoor levels of asbestos in these homes compared with outdoors. Monitoring on a routine basis is intended to determine whether such materials can present a risk to residents. Testing was done during the winter of 1986 and spring of 1987. An enforcement policy became effective December 23, 1986, requiring labeling of all consumer products containing intentionally added asbestos that, under reasonably foreseeable conditions of handling and use, are likely to release fibers. The Commission, in 1989, denied a petition to ban limestone products containing more than 0.1% tremolite because there were no data indicating the presence of asbestiform tremolite in these products and no data indicating that non-asbestiform tremolite is hazardous.

EPA regulates asbestos under the Clean Air Act (CAA), Clean Water Act (CWA), Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), Resource Conservation and Recovery Act (RCRA), Safe Drinking Water Act (SDWA),

Superfund Amendments and Reauthorization Act (SARA), and Toxic Substances Control Act (TSCA). A reportable quantity (RQ) of 1 lb has been established for asbestos under CERCLA. Under CWA, EPA has set the maximum contaminant level (MCL) and the maximum contaminant level goal (MCLG) for asbestos at 7 million fibers per liter. Under TSCA, EPA prohibits the manufacture and use of asbestos in certain products. Also under TSCA, EPA has promulgated standards covering asbestos abatement project personnel not covered under OSHA standards. A voluntary EPA program is removing or encapsulating sources of asbestos release in school buildings. Asbestos is subject to reporting requirements under CERCLA, RCRA, SARA, and TSCA.

FDA regulates, under the Food, Drug, and Cosmetic Act (FD&CA), the use of asbestos in indirect food additives, adhesives, components of coatings, and polymers. FDA has also taken action concerning asbestos, restricting the utilization of asbestos filters in the manufacture of drugs and drug ingredients.

The NIOSH/OSHA Asbestos Work Group recommended that consideration be given to lowering the OSHA permissible exposure limit (PEL) to the lowest level detectable. This group stated that the level should be 100,000 fibers/m^3 (greater than 5 μm in length), in a 400-liter air sample, as an 8-hr TWA. The group also recommended the following definition of asbestos:

"Asbestos is defined to be chrysotile, crocidolite, and fibrous cummingtonites grunerite including amosite, fibrous tremolite, fibrous actinolite, and fibrous anthophyllite. The fibrosity of the above minerals is ascertained on a microscopic level with fibers defined to be particles with an aspect ratio of 3:1 or larger."

The OSHA PEL for asbestos fibers in the workplace is 0.1 fibers/cm^3 of air as an 8-hr TWA for fibers longer than 5 μm. This standard also requires personal protective equipment, training, medical surveillance, signs, labeling, and engineering controls.

OSHA published an Emergency Temporary Standard (ETS), lowering the PEL TWA for ambient asbestos to 0.5 fibers/cm^3. Enforcement of the ETS was stayed by the Fifth Circuit Court of Appeals. OSHA then published a supplemental proposal to the ETS. This supplement contained an additional option for a PEL of 0.2 fibers/cm^3 (5 μm or longer). OSHA regulates asbestos as a chemical hazard in laboratories under the Hazard Communication Standard. Regulations are summarized in Volume II, Table A-6.

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