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 2004). Nearly everyone's life has been directly or indirectly affected by cancer. Most scientists involved in cancer research believe that the environment in which we live and work may be a major contributor to the development of cancer (Lichtenstein *et al.* 2000). In this context, the "environment" is anything that people interact with, including exposures resulting from lifestyle choices, such as what we eat, drink, or smoke; natural and medical radiation, including exposure to sunlight; workplace exposures; drugs; socioeconomic factors that affect exposures and susceptibility; and substances in air, water, and soil (OTA 1981, IOM 2001). Other factors that play a major role in cancer development are infectious diseases, aging, and individual susceptibility, such as genetic predisposition (Montesano 2001). We rarely know what environmental factors and conditions are responsible for the onset and development of cancers; however, we have some understanding of how some types of cancer develop, especially cancers related to certain occupational exposures or the use of specific drugs. Many experts 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 relationship 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 (i.e., to be carcinogenic). Section 301(b)(4) of the Public Health Service Act, as amended, 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 (RoC) is an informational scientific and public health document that identifies and discusses agents, substances, mixtures, or exposure circumstances that may pose a hazard to human health by virtue of their carcinogenicity. It serves as a meaningful and useful compilation of data on (1) the carcinogenicity (ability to cause cancer), genotoxicity (ability to damage genes), and biologic mechanisms (modes of action in the body) of the listed substances in humans and/or in animals, (2) the potential for human exposure to these substances, and (3) Federal regulations to limit exposures. The RoC does not present quantitative assessments of the risks of cancer associated with these substances. Thus listing of substances in the RoC only indicates a potential hazard and does not establish the exposure conditions that would pose cancer risks to individuals in their daily lives. Such formal risk assessments are the responsibility of the appropriate federal, state, and local health regulatory and research agencies.

The substances listed in the RoC are either known or reasonably anticipated to cause cancer in humans in certain situations. With many listed substances, cancer may develop only after prolonged exposure. For example, smoking tobacco is known to cause cancer in humans, but not all people who smoke develop smoking-related cancer. With some substances or exposure circumstances, however, cancer may develop after even brief exposure. Examples include certain occupational exposures to asbestos or bis(chloromethyl) ether. The cancer hazard that listed substances pose to any one person depends on many factors. Among these are the intrinsic carcinogenicity of the substance, the amount and duration of exposure, and an individual's susceptibility to the carcinogenic action of the substance. Because of these considerations, the RoC does not attempt to rank substances according to the relative cancer hazards they pose.

Potential Beneficial Effects of Listed Carcinogens

As stated above, the purpose of the RoC is to identify hazards to human health posed by carcinogenic substances; therefore, it is not within the scope of this report to address potential *benefits* of exposure to certain carcinogenic substances in special situations. For example, numerous drugs typically used to treat cancer or other medical conditions have been shown to increase the frequency of primary or secondary cancers in patients undergoing treatment for specific diseases. In these cases, the benefits of using the drug to treat or prevent a specific disease outweigh the added cancer risks associated with its use. Personal decisions concerning voluntary exposure to carcinogenic substances should be based on information that is beyond the scope of the RoC. Individuals should not make decisions concerning the use of a given drug, or any other listed substance, based solely on the information contained in the RoC. Such decisions should be made only after consultation 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 may cause cancer. Much 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 the RoC. Many of the listed substances 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 laboratory animal studies are used to evaluate whether substances are possible human carcinogens. The strongest evidence for establishing a relationship between exposure to any given substance and cancer in humans comes from epidemiological studies—studies of the occurrence of a disease in a defined population and the factors that affect its occurrence (Bradford 1971). Epidemiological studies of human exposure and cancer are difficult (Rothman 1986). They must rely on natural, not experimental, human exposures and must therefore consider many factors that may affect cancer prevalence besides the exposure under study. One such factor is the latency period for cancer development. The exposure to a carcinogen often occurs many years (sometimes 20 to 30 years or more) before the first sign of cancer appears. Another valuable method for identifying substances as potential human carcinogens is the long-term animal bioassay. These studies provide accurate information about dose and duration of exposure and they are less affected than epidemiology studies by possible interaction of the test substance with other chemicals or modifying factors (Huff 1999). In these studies, the substance is given to one or (usually) two species of laboratory rodents over a range of doses for nearly the animals' entire lives.

Experimental cancer research is based on the scientific assumption that substances causing cancer in animals will have similar effects in humans. It is not possible to predict with complete certainty from

animal studies alone which substances will be carcinogenic in humans. However, known human carcinogens that have been tested adequately in laboratory animals also cause cancer in laboratory animals (Fung *et al.* 1995). In many cases, a substance first was found to cause cancer in animals and later confirmed to cause cancer in humans (Huff 1993). How laboratory animals respond to substances, including developing cancer and other illnesses, does not always strictly correspond to how people will respond. Nevertheless, laboratory animal studies remain the best tool for detecting potential human health hazards of all kinds, including cancer (OTA 1981, Tomatis *et al.* 1997).

Listing Criteria

The criteria for listing an agent, substance, mixture, or exposure circumstance in the RoC are as follows:

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.

*This evidence can include traditional cancer epidemiology studies, data from clinical studies, and/or data derived from the study of tissues or cells from humans exposed to the substance in question that can be useful for evaluating whether a relevant cancer mechanism is operating in people.

The listing criteria presented here were first adopted for use in the *Eighth Report on Carcinogens*, which was published in 1998. The clarification noted above was issued in a *Federal Register* notice dated April 2, 1999 (see 64FR15983-15984, see also *Federal Register* notice dated April 19, 1999: 64FR 19188-19189). Listing criteria for substances listed in earlier editions of the RoC are outlined in the introductions to those editions.

Preparation of the RoC

Within the DHHS, the Secretary has delegated the responsibility for preparing the RoC to the National Toxicology Program (NTP). The process used to prepare the RoC involves several levels of review of the nominations considered for listing in or delisting (removal) from the report. Opportunities for public comment and participation are an integral part of the review 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 Update newsletter, and other appropriate publications. The NTP actively solicits nominations from member agencies of the NTP Executive Committee.[1] Nominations for the RoC also come from reviews of the literature performed by the NTP. Potential nominations are identified from such sources as the NTP Technical Reports, the IARC *Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, the California Environmental Protection Agency's Carcinogen List, and other similar sources.

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

The nominations for listing in the *Eleventh Report on Carcinogens* initially were evaluated by a Report on Carcinogens Review Committee (RG1), composed of scientists from the National Institute of Environmental Health Sciences. For each nomination, the RG1 determined whether the information available was sufficient for applying the criteria for listing and whether the nomination warranted formal consideration by the NTP. This committee received the information submitted with each nomination and any relevant supplemental materials identified by RoC staff. For each nomination the committee reviewed this information and made a formal recommendation to the Director, NTP, either to continue with the formal review for listing or delisting or not to pursue the nomination at that time. The criterion for not pursuing a nomination was the lack of sufficient information for applying the listing criteria. Those nominations not accepted for review were returned to the original nominator who was invited to resubmit the nomination with additional justification, such as new cancer data or exposure information. The NTP Executive Committee and the NTP Board of Scientific Counselors were informed of all nominations not accepted for review.

Upon approval of the nominations by the Director, the NTP announced its intent to review the nominations for the *Eleventh Report on Carcinogens* and solicited public comment on all nominations through announcements in the *Federal Register* and NTP publications. The NTP then initiated an independent search and

[1]Agencies represented on the NTP Executive Committee include: 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 Environmental Health (NCEH/CDC), 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).

review of the scientific literature and prepared a background document for each nomination under consideration. The comments received in response to the public announcement were used to help identify issues that should be addressed in the background documents. Whenever possible, the background documents were prepared with the assistance of a consultant or a panel of consultants with recognized expertise on the nomination.

The RG1 then conducted the initial scientific review of a nomination for listing in the *Eleventh Report on Carcinogens*. The RG1 first reviewed the background document prepared for each nomination and determined whether it was adequate for use in reviewing the nomination and applying the criteria for listing in the RoC. After acceptance of the background document the RG1 then proceeded with scientific review of the nomination. It considered the information in the background document and all public comments received in response to the announcement of the nomination, and made a formal recommendation to the NTP Director for its listing in the RoC. Upon acceptance of the background document by the RG1, it was considered the final document of record and was placed on the NTP RoC web site with a notice published on the NTP list-serv and the NTP home web site announcing its availability.

The NTP Executive Committee's Interagency Working Group for the Report on Carcinogens (RG2), a governmental interagency scientific review group, conducted a second review of the nominations. For each nomination, the RG2 assessed whether relevant information was available and sufficient for its listing in the RoC. The RG2 considered the original nomination, the background document, and all public comments received in response to announcements of the nominations. Upon completion of its review, the RG2 made its formal recommendations to the NTP Director for listing the nominations in the RoC.

The third review of the nominations was an independent external scientific peer review by a standing subcommittee of the NTP Board of Scientific Counselors (the RoC Subcommittee). The RoC Subcommittee assessed whether the relevant information available for each nomination was sufficient for its listing in the RoC. This review was conducted in an open public meeting. A notice of the review announcing the meeting and the availability of the background documents, and soliciting public comment on the nominations was published in the *Federal Register* and NTP publications. The notice invited interested groups or individuals to submit written comments and/or address the RoC Subcommittee during the public meeting. Upon completion of its review, the RoC Subcommittee made its formal recommendations to the NTP Director for listing the nominations in the RoC.

Following completion of the reviews by the RG1, RG2 and RoC Subcommittee, the NTP published the nominations and the review groups' recommendations for each nomination in the *Federal Register,* and solicited the third and final round of public comment and input on the nominations.

The recommendations of the RG1, RG2, and RoC Subcommittee and all public comments received were presented to the NTP Executive Committee for review and comment. The NTP Executive Committee reviewed the information on each nomination and provided to the NTP Director a recommendation on its listing in the RoC.

The NTP Director received the independent recommendations of the RG1, RG2 and RoC Subcommittee, the opinion of the NTP Executive Committee, and all public comments concerning the nominations. The NTP Director evaluated this input and any other relevant information on the nominations and developed recommendations to the Secretary, DHHS regarding whether to list or not to list the nominations in the RoC.

The NTP prepared the final draft of the RoC based on the NTP Director's recommendations and submitted it to the Secretary, DHHS, for review and approval. Upon approval of the RoC, the Secretary submitted it to the U. S. Congress as a final document. Submittal of the RoC to Congress constituted publication of the report, and it became available to the public at that time. The NTP published a notice of the publication and availability of the Eleventh Edition of the RoC, indicating all newly listed agents, substances, mixtures or exposure circumstances in the *Federal Register* and NTP publications.

Estimation of Exposure

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

The RoC also is required to provide information about the nature of exposures and the estimated numbers of people exposed to listed substances. Four of the agencies participating with the NTP in preparation of the *Eleventh Report on Carcinogens*—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 on use, production, and exposure in each entry of the RoC was reviewed by staff members from these four regulatory agencies. Because little information typically is available, estimating the number of people who could be exposed, and the route, intensity, and duration of exposure for each substance is a very difficult task. This RoC attempts to respond to these questions, and adequate answers that could be obtained are included in the individual profiles for each listing.

The National Institute for Occupational Safety and Health (NIOSH) has conducted two occupational exposure surveys: the National Occupational Hazard Survey (NOHS), conducted from 1972 to 1974, and the National Occupational Exposure Survey (NOES), conducted from 1981 to 1983. These surveys yielded data on potential exposure to many listed substances. Although dated, NOES estimates are provided in the profiles of the listings when available, and NOHS figures are given in some profiles if no other exposure data were available.

Regulations and Guidelines

The RoC is required to identify each listed substance for which no standard for exposure or release into the environment has been established by a Federal Agency. The *Eleventh Report on Carcinogens* addresses this requirement by providing in each profile a summary of the regulations and guidelines that are likely to decrease exposure to that substance. Some of these regulations and guidelines have been enacted for reasons other than the substance's carcinogenicity (*for example*, to prevent adverse health effects other than cancer or to prevent accidental poisoning of children). These regulations are included in the profiles, because reduction of exposure to a carcinogen will likely reduce the risk for cancer. In earlier editions of the RoC, each profile contained a summary of relevant regulations with a cumulative list of the *Code of Federal Regulations* and *Federal Register* citations for each listing published in a separate volume. All regulations have been researched and presented in the *Eleventh Report on Carcinogens* using a new format. Starting with this edition, the regulations for a listing are organized by regulatory agencies and major acts, and are provided at the end of the profile rather than in a separate volume.

The majority of the regulations cited in the RoC were enacted by the following federal agencies: CPSC, the U.S. Department of Transportation, the EPA, the FDA, and OSHA. The guidelines cited

in the RoC are primarily those published by NIOSH and the American Conference of Governmental Industrial Hygienists. Additionally, regulations and guidelines enacted by other governmental agencies not listed above are cited if their likely outcome is to reduce exposure to the substance. It is beyond the scope of this report to provide detailed information or interpretation concerning the implementation of each regulatory act, and no attempt is made to do so. Some commonly used regulatory terms are defined in the glossary (Appendix F), and links to the websites for the *Code of Federal Regulations* and for each of the major regulatory agencies are provided in the reference section of this Introduction for those wishing to obtain additional information on these agencies and their regulations.

Two regulations were identified that apply to all substances listed in the RoC:

1. OSHA's Hazard Communication Standard
   This regulation is intended to communicate the hazards of chemicals and appropriate protective measures to protect employees. The program includes maintenance of a list of hazardous chemicals, labeling of containers in the workplace, and preparation and distribution of material safety data sheets to employees. The rule states that chemicals shall be considered "hazardous" if they have been listed as a carcinogen or potential carcinogen in (1) the NTP's RoC (latest edition) or (2) the IARC Monographs (latest editions) or (3) OSHA's Occupational Safety and Health Standards, Subpart Z – Toxic and Hazardous Substances.
2. EPA's Criteria for the Evaluation of Permit Applications for Ocean Dumping of Materials under the Toxic Substances Control Act (TSCA)
   This regulation prohibits ocean dumping of materials containing "known carcinogens, mutagens, or teratogens or materials suspected to be carcinogens, mutagens, or teratogens by responsible scientific opinion" as other than trace contaminants.

Because both of these regulations apply to all substances listed in the RoC, they are not identified individually in the listing profiles. However, the reader should be aware that these regulations pertain to all substances listed in the RoC, and that their likely outcome is to reduce exposure to listed substances.

Two OSHA regulations identified in some of the listing profiles require clarification:

1. Specific substances are listed as having "comprehensive standards" if, in addition to the permissible exposure limit (PEL), OSHA has regulations for the substance that include provisions for: exposure monitoring, engineering and work practice controls, use of respirators and protective garments and equipment, hygiene facilities, information and training, labeling of substance containers and worker areas in which the substance is used, and health screening programs.
2. The OSHA PEL identified in the profiles for glass wool (respirable size), ceramic fibers (respirable size), and wood dust are based on the standard for Particulates Not Otherwise Regulated (PNOR). This standard sets limits applicable to all inert or nuisance dusts, whether mineral, inorganic, or organic, not identified specifically by substance name. OSHA recommended that the profiles for these three substances include the PEL established by the PNOR standard.

Estimation of Risk Reduction

For each effluent, ambient, or exposure standard established by a Federal agency for a listed substance, the RoC is required to state the extent to which, on the basis of available medical, scientific, or other data, the implementation of that standard decreases the public's risk for cancer. This statement requires quantitative information on how much protection from cancer the public is afforded by established Federal standards.

Estimating the extent to which listing a substance in the RoC protects public health is perhaps the most difficult task in preparing the RoC. The carcinogenic risk (i.e., the probability of developing cancer) depends on many things, including the intensity, route, and duration of exposure to a carcinogen. People may respond differently to similar exposures, depending on their age, sex, nutritional status, overall health, genetics, and many other factors. Only in a few instances can risk for cancer be estimated with complete confidence, and these estimations require studies of long-term human exposures and cancer incidence in restricted environments, which rarely are available.

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 presumes that data exists on past and present exposure levels, or that all workplace conditions comply with regulations. It is rare that one has information supporting these assumptions. Despite these limitations, it is reasonable and prudent to accept that reducing exposure, for any reason, particularly to substances shown to be carcinogenic in experimental animals, will decrease the incidence of cancer in people (Tomatis *et al.* 1997, Montesano *et al.* 2001). This relationship is the basis of current regulatory policies that aim to lower human exposure to cancer-causing substances, and thereby, improve public health.

Major environmental pollution prevention acts, such as the EPA's Resource Conservation and Recovery Act, Clean Water Act and Clean Air Act, were passed in the early 1970s. These laws have lead to the reduction in exposure to a number of substances listed in the RoC. Although one can not draw a direct cause and effect relationship between pollution reduction and cancer incidence, recent data from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute show decreasing cancer trends for many cancers, although others are increasing (SEER 2003). The "Annual Report to the Nation on the Status of Cancer, 1975-2000" (Wier *et al.* 2003) is based in part on the most recent SEER data and provides an update on cancer mortality (death rates), incidence rates (new cases), and trends in the United States. The report is issued annually by the Centers for Disease Control and Prevention (CDC), the American Cancer Society (ACS), the National Cancer Institute (NCI) of the National Institutes of Health, and the North American Association of Central Cancer Registries (NAACCR). This report indicates that overall, cancer death rates (for men and women combined) were stable from 1998 through 2000 - that is, rates neither increased nor decreased. Before this time, death rates increased through 1990, stabilized through 1994, and declined from 1994 through 1998. Throughout the late 1990s, trends for women stabilized, while death rates for men continued to decline. Lung, colorectal, breast and prostate cancers have the highest prevalence in the United States and account for more than half of all cancer cases:

- Lung cancer is the leading cause of death from cancer in men and women in the United States. Lung cancer death rates among white and black men declined throughout the 1990s, while the rate of increase in deaths among women slowed during the same period, reflecting reductions in tobacco smoking. It is interesting to note that recently published studies have shown a rise in lung cancer and cardiopulmonary disease due to air pollution (Montesano *et al.* 2001).
- Colorectal cancer death rates have been declining for both white and black men and women beginning in the 1970s, with steeper declines beginning in the mid-1980s. This decline is attributed to better screening and treatment methods for this cancer.

- Breast cancer death rates continue to fall despite a gradual, long-term increase in incidence rates. Decreasing rates in deaths from breast cancer and increasing incidence rates during the 1990s have been attributed, in part, to increased use of mammography screening and the availability of improved therapies.
- Prostrate cancer death rates have been declining since 1994, while incidence rates have been rising since 1995, with a 3.0 percent per year increase in incidence in white men and a 2.3 percent per year increase in black men. No currently recognized risk factors account for the decline in prostate cancer mortality, although the decrease might reflect improvements in treatment combined with improved detection using a blood test for prostate specific antigen (PSA).

Cancer sites without significant improvement in survival rates in the past 25 years include the uterine corpus, cervix, larynx, liver, lung, pancreas, stomach, and esophagus (Jemal *et al.* 2004).

Cancer incidence rates for all types of cancer combined increased from the mid-1970s through 1992, declined from 1992 through 1995, and then stabilized (a non-significant increase) from 1995 through 2000. Increases in incidence rates in breast cancer and prostate cancer offset long-term decreases in lung cancer in men (Wier *et al.* 2003). The SEER data also indicate that the incidences of liver, thyroid, melonoma of the skin and kidney cancers increased over the time interval between 1992 ad 2000 (SEER 2003).

Listing Substances in the *Eleventh Report on Carcinogens*

The *Eleventh Report on Carcinogens* contains 246 entries, 17 of which have not appeared in earlier editions of the RoC.

The *Eleventh Report on Carcinogens* lists lead and lead compounds as *reasonably anticipated to be human carcinogens.* This listing of lead and lead compounds supersedes the listings of individual lead compounds (including lead acetate and lead phosphate) in previous editions of the RoC and applies to lead and all lead compounds.

The heterocyclic amines 2-amino-3,4-dimethylimidazo[4,5-*f*]quinoline (MeIQ), 2-amino-3,8-dimethylimazo[4,5-*f*]quinoxaline (MeIQx), and 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP), are listed for the first time in the *Eleventh Report on Carcinogens* as *reasonably anticipated to be human carcinogens*. Another heterocyclic amine, 2-amino-3-methylimidazo [4,5-*f*]quinoline (IQ) was listed in the *Tenth Report on Carcinogens*, also as *reasonably anticipated to be a human carcinogen.* These four listings have been grouped together as a family under the title "Selected Heterocyclic Amines." The listing first gives evidence for the carcinogenicity for each heterocyclic amine separately, and then presents a combined section that discusses other information relevant to carcinogenicity, properties, use, production, exposure and regulations.

Three types of ionizing radiation (X-radiation, gamma radiation, and neutrons) are listed as *known to be human carcinogens* for the first time in the *Eleventh Report on Carcinogens*. The radioactive compound thorium dioxide, which decays by emission of alpha particles, was first listed in the *Second Annual Report on Carcinogens* (1981). Radon and its most common isotopic forms (radon-220 and radon-222), which also emit primarily alpha particles, were first listed in the *Seventh Annual Report on Carcinogens* (1994). The profiles for these sources of ionizing radiation have been placed together as a family of profiles under the title "Ionizing Radiation."

Diethanolamine was nominated for possible listing in the *Eleventh Report on Carcinogens*, but after a formal scientific review of all relevant information pertaining to its possible carcinogenicity, was not recommended for listing. The basis for the recommendation not to list diethanolamine is summarized in Appendix C of the *Eleventh Report on Carcinogens*.

Section II lists the names of all the agents, substances, mixtures, or exposure circumstances listed in the *Eleventh Report on Carcinogens*. It has two parts: Section II.A identifies 58 substances as *known to be human carcinogens*, and Section II.B identifies 188 substances as *reasonably anticipated to be human carcinogens*.

Section III, Substance Profiles, contains a brief description of each substance with a summary of the evidence for its carcinogenicity; relevant information on properties, use, production and exposure; and a summary of the regulations and guidelines that are likely to decrease the exposure to the substance. These profiles are in alphabetical order and include references to scientific literature used to support the listings.

The substances listed in the *Eleventh Report on Carcinogens* may constitute only a fraction of actual human carcinogens. The RoC lists only those nominated agents, substances, mixtures or exposure circumstances for which relevant data exist and have been reviewed and found to meet the listing criteria defined above. As additional substances are nominated, they will be considered and reviewed for possible listing in future editions of the RoC.

Certain manufacturing processes, occupations, and exposure circumstances have been considered by IARC and are classified by that agency as known to be carcinogenic to humans because of associated increased incidences of cancer among workers in these settings. However, 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. The NTP has not yet reviewed the data supporting the listing of these occupational situations as posing a cancer hazard. In the interest of public health and for completeness, these occupational exposures are identified in Appendix A of the RoC with the corresponding IARC references.

Other Information Provided in this RoC

Section IV provides tables listing requests to the DHHS for research, testing, and other information relating to carcinogenicity, either from other Federal agencies or from within the DHHS, and how the DHHS responded to the requests. Section V details the listing and delisting procedures for the RoC.

The *Eleventh Report on Carcinogens* also includes seven appendices and an index:

- Appendix A lists manufacturing processes, occupations, and exposure circumstances classified by IARC as known to be carcinogenic to humans.
- Appendix B lists the agents, substances, mixtures, or exposure circumstances that have been delisted from the RoC.
- Appendix C lists the agents, substances, mixtures, or exposure circumstances that have been reviewed but not recommended for listing in the RoC.
- Appendix D lists participants who collaborated in preparing the *Eleventh Report on Carcinogens*.
- 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 RoC.
- The index (a feature introduced in the *Eleventh Report on Carcinogens*) allows the user to search for listings by commonly used synonyms or abbreviations included in the profiles or by CAS Registry Numbers of chemical substances discussed in the profiles.

The eleventh edition of the RoC was prepared following procedures that maximized the quality, objectivity, utility and integrity of the information contained in the report. Although not anticipated, factual errors or omissions in this report may be identified after its distribution. If this should happen, these errors or omissions will be addressed by the NTP. Where appropriate, corrections will initially be posted on the RoC web site at http://ntp-server.niehs.nih.gov/NewHomeRoc/AboutRoC.html and then made in the next edition of

the RoC. For more information on the Eleventh Edition of the RoC, including how to order a printed copy or access it on the Internet, visit the NTP RoC web site at the address above or contact Dr. C. W. Jameson, Head, Report on Carcinogens, National Toxicology Program, MD EC-14, P.O. Box 12233, Research Triangle Park, NC 27709; telephone (919) 541-4096; fax (919) 541-0144; e-mail jameson@niehs.nih.gov.

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