

13th

Report on Carcinogens

2014



U.S. Department of Health and Human Services
Public Health Service
National Toxicology Program

Pursuant to Section 301 (b) (4) of the Public Health
Service Act as amended by Section 262, PL 95-622

Introduction

The probability that a resident of the United States will develop cancer at some point in his or her lifetime is approximately 1 in 2 for men and 1 in 3 for women (ACS 2014). 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 (Reuben 2010). 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, Hanna and Coussens 2001). Other factors that play a major role in cancer development are infectious diseases, aging, and individual susceptibility, such as genetic predisposition (Montesano and Hall 2001). Many experts firmly believe that much of the cancer associated with the environment may be avoided (Reuben 2010).

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, requires that the Secretary of the Department of Health and Human Services (DHHS) publish a biennial report that contains the following information:

- 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.
- Information concerning the nature of such exposure and the estimated number of persons exposed to such substances.
- 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.
- 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 respond 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 (hereinafter referred to as "substances") that may pose a cancer hazard to humans. For each listed substance, the RoC contains a substance profile which provides information on (1) the listing status, (2) cancer studies in humans and animals, and often studies of biologic mechanisms and other data relevant to carcinogenicity, (3) the potential for human exposure to these substances, and (4) Federal regulations to limit exposures.

The substances listed in the RoC are either known or reasonably anticipated to cause cancer in humans in certain situations. A listing in the RoC does not by itself establish that a substance will cause cancer in an individual. Many factors, including the intrinsic carcinogenicity of the substance, the amount and duration of exposure, and the individual's susceptibility to the carcinogenic action of the substance, affect whether a person will or will not develop cancer. The RoC does not attempt to rank substances according to the relative cancer hazards they pose or present quantitative assessments of the

risks of cancer associated with these substances. Such formal risk assessments are the responsibility of the appropriate Federal, state, and local health regulatory and research agencies.

As stated above, the purpose of the RoC is to identify cancer hazards to human health; 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 cancer (i.e., cancer located in the organ or tissue where it originated) or secondary cancer (i.e., cancer that has spread from its organ or tissue of origin to other parts of the body) in patients undergoing treatment for specific diseases. In these cases, the benefits of using the drug to treat or prevent a specific disease may outweigh the added cancer risk associated with its use. Personal decisions concerning voluntary exposure to carcinogenic substances should be made only after consultation with a physician or other appropriate specialist, and not based solely on the information contained in the RoC.

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 the 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 World Health Organization's International Agency for Research on Cancer (IARC), in Lyon, France, and other international agencies, as well as the Environmental Protection Agency of the State of California and U.S. federal agencies, such as the U.S. Environmental Protection Agency.

Studies in both humans and experimental animals are used to evaluate whether substances are potentially carcinogenic in humans. Other studies that may elucidate possible mechanisms of action of potential carcinogens also are considered in the evaluations. 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 human population and the factors that affect its occurrence (Hill 1971). Interpretation of epidemiological studies of human exposure and cancer can be difficult, as they must rely on natural, not experimental, human exposure and must therefore consider many factors that may affect cancer incidence in addition to the exposure under study (Rothman *et al.* 2012). One such factor is the latency period for cancer development (i.e., the time between first exposure to a carcinogen and development of cancer). The first sign of cancer often appears many years (sometimes 20 to 30 years or more) after exposure to the carcinogen. Epidemiological studies of workers exposed to high levels of chemicals have led to the identification of many carcinogens in the United States (Fontham *et al.* 2009).

Another valuable method for identifying substances as potential human carcinogens is the long-term bioassay in experimental animals. These studies provide accurate information about dose and duration of exposure, and they are less affected than epidemiological studies by possible interactions of the test substance with other chemicals or modifying factors (Huff 1999). Experimental cancer research is based on the scientific assumption that substances causing cancer in animals will have similar effects in humans; however, it is not possible to predict with complete certainty from animal stud-

ies alone which substances will be carcinogenic in humans. Known human carcinogens have also been shown to cause cancer in experimental animals when tested adequately (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, 1999). How experimental animals respond to substances, including developing cancer or other illnesses, does not always strictly correspond to how people will respond. Nevertheless, experimental animal studies remain a valuable tool for detecting potential human health hazards of all kinds, including cancer (OTA 1981, Tomatis *et al.* 1997).

In addition to the use of studies in humans and experimental animals, alternative testing methods that incorporate advances in molecular toxicology, computational sciences, and information technology are being developed to prioritize substances for carcinogenicity testing and reduce the use of animals in testing. A 2007 report by the National Academy of Science's National Research Council, *Toxicity Testing in the 21st Century* (NRC 2007), outlined strategies for new approaches, and a research collaboration among the National Toxicology Program (NTP), the U.S. Environmental Protection Agency (EPA), the National Center for Advancing Translational Sciences, and the U.S. Food and Drug Administration (FDA) was established to evaluate whether high-throughput/high-content *in vitro* screening assays, alternative animal models using, for example, zebrafish (*Danio rerio*) and the roundworm *Caenorhabditis elegans*, and computational toxicology approaches can be used initially to facilitate prioritization of chemicals for further testing and ultimately to enable more effective predictions of carcinogenic risk of substances to humans (Collins *et al.* 2008).

Preparation of the RoC

The NTP prepares the RoC on behalf of the Secretary of Health and Human Services. For the preparation of the *Thirteenth Report on Carcinogens*, the NTP followed a four-part process (<http://ntp.niehs.nih.gov/go/rocprocess>) using established criteria (see Listing Criteria, below). New to the process for the *Thirteenth Report on Carcinogens* is the preparation of an RoC Monograph for each substance selected for review for the RoC. The process provides numerous opportunities for public comment, input from external scientists and government scientists, and peer review of the scientific information. Details of the process are described in the section of the RoC entitled Process for Preparation of the Report on Carcinogens.

Listing Criteria

The criteria for listing an agent, substance, mixture, or exposure circumstance in the RoC are shown in the box on this page. The listing criteria presented here were first adopted for use in the *Eighth Report on Carcinogens*, which was published in 1998. The listing criteria were clarified the following year in two *Federal Register* notices (NTP 1999a,b). Listing criteria for substances listed in earlier editions of the RoC are outlined in the introductions to those editions.

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. 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 is also required to provide information about the nature of exposures and the estimated numbers of people exposed to listed substances. Because little information typically is available, estimating the number of people who could be exposed and the route,

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, which can be useful for evaluating whether a relevant cancer mechanism is operating in humans.

intensity, and duration of exposure for each substance is a difficult task. However, other types of information, such as data on use, production, occupational exposure, and exposure from environmental release or occurrence, can be used to determine whether there is (or was) exposure in the United States, and this information is included in each substance profile. 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 provided if no other exposure data are available.

Regulations and Guidelines

The RoC is required to identify each of the listed substances for which no standard for exposure or release into the environment has been established by a Federal agency. The RoC addresses this requirement by providing in each profile a summary of the regulations and guidelines, if any, that are likely to decrease human exposure to that substance. Some of these regulations and guidelines have been enacted for reasons other than the substance's carcinogenicity (e.g., 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 suspected or known carcinogen is likely to reduce the risk for cancer. Regulations are organized by regulatory agencies and the acts enforced by those agencies, and are provided at the end of each profile.

Four of the agencies participating with the NTP in preparation of the *Thirteenth Report on Carcinogens* — the Consumer Product Safety Commission (CPSC), EPA, FDA, and Occupational Safety and Health Administration (OSHA) — are responsible for regulating hazardous substances and limiting the exposure to and use of such substances, and the majority of the regulations cited in the RoC were enacted by those agencies. The guidelines cited in the RoC are primarily those published by NIOSH and the American Conference of Governmental Industrial Hygienists. In addition, regulations and guidelines enacted by other governmental agencies 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, which follows the Substance Profiles. Links to the Web sites for the *Code of Federal Regulations* and for each of the major regulatory agencies are provided at the end of the Reference section of this Introduction for those wishing to obtain additional information on these agencies and their regulations.

An OSHA regulation identified in some of the listing profiles requires clarification. 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. The sets of comprehensive standards are provided in 29 CFR 1910 Subpart Z and also on the OSHA Web site.

Some specific regulatory actions may depend on the listing of a substance in the RoC. Information on three such actions, which potentially apply to all or a substantial subset of the listing of substances in the RoC, are not identified individually in the listing profiles, but are described below. Two regulations — the OSHA Hazard Communication Standard and the EPA Criteria related to ocean dumping — apply or potentially apply to all substances listed in the RoC, because that is one of several criteria that may be used to classify a substance as a carcinogen according to the regulations. The third regulation, under the Toxic Substances Control Act (TSCA), applies to certain listed substances because its application depends on both listing in the RoC and in one of several specific lists of chemicals distributed in commerce or meeting other specifications as defined by TSCA.

- *OSHA's Hazard Communication Standard.* This regulation is intended to communicate the hazards of chemicals and appropriate protective measures to protect employees. In 2012, OSHA modified this standard to conform to the United Nations' *Globally Harmonized System of Classification*

and Labelling of Chemicals (GHS). The program includes maintenance of a list of hazardous chemicals, labeling of shipped and workplace containers, preparation and distribution of safety data sheets to employees, and provision of employee training. The rule states that a chemical may be considered a carcinogen or potential carcinogen for hazard communication purposes in lieu of applying the classification criteria described in the standard if it has been listed as a carcinogen or potential carcinogen in current editions of (1) the RoC, (2) the IARC monographs, or (3) OSHA's Occupational Safety and Health Standards, Subpart Z – Toxic and Hazardous Substances.

- *EPA's Criteria for the Evaluation of Permit Applications for Ocean Dumping of Materials under the Toxic Substances Control Act.* 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.
- *TSCA Section 12(b)* export notification requirements apply to those chemicals listed in the RoC that may be distributed in commerce, manufactured, processed, used, or disposed of. Section 12(b) of TSCA requires any person exporting or intending to export to a foreign country a chemical for which data submission is required under TSCA sections 4, 5, 6, or 7 to notify the EPA Administrator of such exportation or intent to export (for more information, see <http://www.epw.senate.gov/tsca.pdf>). The RoC is used to evaluate eligibility for exemptions from these requirements based on *de minimis* concentration levels. Chemicals listed as a carcinogen or potential carcinogen in current editions of (1) the RoC, (2) the IARC monographs, or (3) OSHA's Occupational Safety and Health Standards, Subpart Z – Toxic and Hazardous Substances are not subject to TSCA section 12(b) export notification requirements where such chemicals are present in a concentration of less than 0.1% by weight or volume; however, the *de minimis* concentration level for polychlorinated biphenyls (PCBs) is 50 ppm (for further details see <http://www.gpo.gov/fdsys/granule/FR-2006-11-14/E6-19182> and select Text or PDF from Formats under Download Files).

Cancer Rates and Estimates of Risk Reduction

Cancer is the second leading cause of death in the United States. According to estimates from the American Cancer Society, over 1.6 million new cancer cases and over 580,000 deaths from cancer in the United States are expected to occur in 2014 (ACS 2014). In men, the most common sites of newly diagnosed cancer are the prostate, lung and bronchus, and colorectum (colon and rectum); these three sites account for 49% of all cancer cases, and prostate cancer is the most common (27%). In women, the three most common sites, accounting for 50% of the total, are the breast (29%), lung and bronchus, and colorectum. At present, cancer at these sites also results in the highest death rates: in men, mortality is highest for cancer of the lung and bronchus, followed by the prostate and colorectum; in women, mortality is highest for cancer of lung and bronchus, followed by the breast and colorectum (ACS 2014). Data on cancer incidence and death rates were reported in the *Annual Report to the Nation on the Status of Cancer, 1975–2010* (Edwards *et al.* 2014) and the *Cancer Statistics* report prepared annually by the American Cancer Society (ACS 2014); both reports use the most recent data from

the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute (Howlander *et al.* 2014).

In recent years, overall cancer incidence rates were stable in women from 2006 to 2010 (Siegel *et al.* 2014), while those in men decreased modestly (0.6% per year). These decreases are largely explained by decreased rates of colorectal, prostate, and lung cancer in men. Declines in colorectal cancer rates were similar in women, but the rates for breast cancer were stable from 2006 to 2010, the most recent period for which data were available (ACS 2014). Lung cancer rates declined more rapidly in men than in women, but decreases were observed for women aged 35 to 44 years and 54 to 64 years (Henley *et al.* 2014). Mortality from lung cancer in women decreased by 9% from 2002 to 2010 (Siegel *et al.* 2014). While decreases in overall cancer mortality have been driven by declining death rates for the four major cancer sites for each sex, mortality from other types of cancers has been increasing. Trend analysis for the period from 2001 to 2010 showed increasing death rates for cancers of the oropharynx, anus, liver, pancreas, and soft tissue (including the heart) in men and women and for melanoma in men. Incidence rates increased from 2006 to 2010 for melanoma of the skin, esophageal adenocarcinoma, and cancers of the thyroid, liver, kidney, anus, and pancreas in both men and women, with the largest increases for cancers of the thyroid and liver (Siegel *et al.* 2014).

Of particular concern is that incidence rates of cancer in children in the United States increased at a rate of 0.6% per year from 1975 to 2010 (ACS 2014). For 2014, the American Cancer Society estimated that there would be 10,450 new cancer cases in children under the age of 14 (all races combined) and 5,330 new cases in those aged 15 to 19. The most common cancers in children under 14 are acute lymphocytic leukemia (26%), brain and central nervous system (CNS) cancers (21%), neuroblastoma (7%), and non-Hodgkin lymphoma (6%), while those in children aged 15 to 19 are Hodgkin lymphoma (15%), thyroid carcinoma (11%), brain and CNS cancers (10%), and testicular germ-cell tumors (8%). Children are particularly vulnerable to environmental risk factors, including numerous toxins and detrimental exposures from air, food, water, medicines, pesticides, and ionizing radiation, even before birth (NCI 2010). Despite the increases in incidence rates, death rates for childhood and adolescent cancers declined steadily from 1975 to 2010, by an average of 2.1% per year.

Cancer also has a major economic impact on American society. The costs to American society were estimated by the National Institutes of Health (NIH) to be \$99 billion for direct medical costs in 2009, and these costs more than double if the costs for lost productivity due to illness (estimated at \$19.6 billion) and to premature death (estimated at \$124.8 billion) are included (Reuben 2010). The financial burden resulting from cancer is expected to increase further. The NIH (2013) projects direct cancer care expenditures of \$158 billion in 2020 based on current healthcare costs. If medical costs increase, the financial burden of cancer will be even higher, an estimated \$207 billion in 2020, based on a 5% annual increase in costs.

IARC has predicted that within two decades, cancer deaths worldwide will increase from 8.2 million (in 2012) to 13 million per year, while new cancer cases increase from approximately 14 million to 22 million per year (Stewart and Wild 2014). However, IARC estimated that between one third and one half of all cancer deaths could be prevented by changing behaviors such as reducing use of tobacco, avoiding excessive alcohol consumption, protecting against sunburn, increasing physical activity, and controlling body weight. IARC also noted that reducing exposure to environmental pollution in the water and air by regulatory action and technological improvements would help to reduce the burden of cancer worldwide. IARC expects the future increase in cancer burden to have its greatest impact in low-

and middle-income countries, where some cancers, such as those of the cervix and liver, are already common, and cancer at other sites will increase as a result of demographic changes, as both life expectancy and overall population increase. The cancer profiles of these populations also are expected to change as the populations adopt behavioral and lifestyle habits typical of more affluent, industrialized countries, likely resulting in increases in female breast cancer, prostate cancer, and colorectal cancer.

Approaches to reduction of cancer incidence and mortality include both primary prevention, including the reduction or elimination of exposure, and secondary prevention, including early detection via screening and treatment of any diagnosed precancerous conditions or early malignancies (Bode and Dong 2009). Reduction of tobacco use over the past 50 years is largely responsible for the decrease in lung-cancer mortality in men. About 40% of the decrease in overall cancer mortality in men is due to decreased lung-cancer mortality, indicating that primary prevention has a major impact in improving public health (Siegel *et al.* 2014). For example, a combination of education and social policies, such as excise taxes and smoke-free air laws, contribute to reducing tobacco use. Mortality from lung cancer has decreased more slowly in women because cigarette smoking in women peaked 20 years later than in men. Decreases in mortality from cervical, breast, and colon cancer are thought to have resulted from a combination of early detection and improvements in treatment, although reduction in the use of menopausal hormone therapy among post-menopausal women starting in 2001 may also have contributed to decreases in breast-cancer incidence.

Primary prevention is the basis of current regulatory policies that aim to lower human exposure to cancer-causing substances and thereby improve public health. 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 humans (Tomatis *et al.* 1997, Montesano and Hall 2001). 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 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. Nevertheless, there is evidence that regulations have led to reductions in exposure to a number of substances listed in the RoC and probably have contributed, in part, to the decreases in cancer incidence and mortality observed over the past decade. The reduction in cancer death rates translates to the prevention of approximately 1,340,040 deaths over the 20-year period from 1990 to 2010 (Siegel *et al.* 2014). For example, major environmental pollution prevention acts, such as EPA's Resource Conservation and Recovery Act, Clean Water Act, and Clean Air Act, were passed in the early 1970s. These laws have led to reduced exposure to a number of pollutants. Although no analyses were found to determine whether these regulations have decreased cancer incidences, analyses have shown that they have reduced premature deaths from respiratory

illnesses and heart attacks (EPA 2010). Studies have shown associations between lung-cancer mortality and air pollution; therefore, it seems reasonable that regulations reducing air pollution have also reduced cancer risks (Montesano and Hall 2001, Raaschou-Nielsen *et al.* 2010). U.S. workplace levels of many occupational carcinogens also have been reduced since the 1970s (Fontham *et al.* 2009), and it therefore is presumed that these reductions have prevented occupationally related cancers.

Listing of Substances in the Thirteenth Report on Carcinogens

Each edition of the RoC is cumulative and includes substances newly reviewed in addition to those listed in previous editions. The *Thirteenth Report on Carcinogens* contains profiles for 243 substances, some of which (e.g., Estrogens, Steroidal) consist of a class of structurally related chemicals or agents. These include 56 profiles for substances listed as known to be human carcinogens and 187 profiles for substances listed as reasonably anticipated to be human carcinogens. Profiles for related exposures, such as exposure to various types of ultraviolet radiation, and selected members of chemical families, such as nitroarenes, are often grouped together. There are three new listings and one revised listing. The three newly listed substances, 1-Bromopropane, Cumene, and Pentachlorophenol and By-products of Its Synthesis, all are listed as *reasonably anticipated to be human carcinogens*. *o*-Toluidine, which was first listed in the *Third Annual Report on Carcinogens* in 1983 as *reasonably anticipated to be a human carcinogen*, is now listed as *known to be a human carcinogen*.

The names of all the substances — agents, substances, mixtures, or exposure circumstances — listed in the RoC are given in alphabetical order for the two listing categories. Part A identifies the substances listed in the RoC as *known to be human carcinogens*, and Part B identifies those listed as *reasonably anticipated to be human carcinogens*. The substance profiles contain (1) a brief description of each substance, with a summary of the evidence considered key for its carcinogenicity, (2) relevant information on properties, use, production, and exposure, and (3) a summary of the regulations and guidelines that are likely to decrease exposure to the substance. The profiles include references to scientific literature used to support the listings. The substances listed in the RoC do not include all 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.

Other Information Provided in the Thirteenth Report on Carcinogens

Following the Substance Profiles, additional information is provided about terms that are used frequently in the profiles, including a Glossary, a list of Acronyms and Abbreviations, and Units of Measurement. In addition, the following appendices are provided:

- Appendix A provides a list of manufacturing processes, occupations, and exposure circumstances classified by IARC as 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 identifies participants who collaborated in preparation of the *Thirteenth Report on Carcinogens*.

- Appendix E provides a link to a searchable database of substances nominated to the NTP for toxicological testing.
- Appendix F is a cross-referenced list of substances and their common synonyms or abbreviations.
- Appendix G lists, by Chemical Abstract Service (CAS) Registry number, all of the chemicals included in the RoC for which CAS Registry numbers were identified.

The *Thirteenth Report on Carcinogens* 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 NTP Office of the Report on Carcinogens Web site at <http://ntp.niehs.nih.gov/go/roc> and then made in the next edition of the RoC.

For more information on the *Thirteenth Report on Carcinogens*, visit the NTP Office of the Report on Carcinogens Web site at the link provided above or contact Dr. Ruth Lunn, Director, Office of the Report on Carcinogens, National Toxicology Program, MD K2-14, P.O. Box 12233, Research Triangle Park, NC 27709; telephone (919) 316-4637; fax (301) 480-2970; e-mail lunn@niehs.nih.gov.

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- American Conference of Governmental Industrial Hygienists (ACGIH)
<http://www.acgih.org/home.htm>
- Code of Federal Regulations (CFR), U.S. Government Printing Office
<http://www.gpoaccess.gov/cfr/index.html>
- Consumer Product Safety Commission (CPSC)
<http://www.cpsc.gov>
- Department of Transportation (DOT)
<http://www.dot.gov>
- Environmental Protection Agency (EPA)
<http://www.epa.gov>
- Integrated Risk Information System
<http://cfpub.epa.gov/ncea/iris/index.cfm>
- Food and Drug Administration (FDA)
<http://www.fda.gov>
- Center for Food Safety & Applied Nutrition
<http://www.fda.gov/aboutfda/centersoffices/officeoffoods/cfsan/default.htm>
- International Agency for Research on Cancer (IARC).
<http://www.iarc.fr>
- Monographs on the Evaluation of Carcinogenic Risks of Chemicals to Humans
<http://monographs.iarc.fr/index.php>
- National Institute for Occupational Safety and Health (NIOSH)
<http://www.cdc.gov/niosh>
- Pocket Guide to Chemical Hazards
<http://www.cdc.gov/niosh/npg>
- NIOSH Safety and Health Topic – Cancer
<http://www.cdc.gov/niosh/topics/cancer>
- NIOSH Carcinogen List
<http://www.cdc.gov/niosh/topics/cancer/npotocca.html>
- National Toxicology Program (NTP)
<http://ntp.niehs.nih.gov>
- Report on Carcinogens
<http://ntp.niehs.nih.gov/go/roc>
- Occupational Safety and Health Administration (OSHA)
<http://www.osha.gov>