15th Report on Carcinogens

2021

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 Objective of the Report on Carcinogens

The Report on Carcinogens (RoC) is a scientific and public health document that identifies and discusses agents, substances, mixtures, or exposure circumstances (referred to in the report as "substances") that may pose a cancer hazard to humans. As the identification of carcinogens is a key step in cancer prevention, publication of the RoC represents an important government activity towards improving public health.

The Burden of Cancer

Cancer — a group of diseases characterized by uncontrolled growth and spread of abnormal cells that can result in death if not controlled — affects almost everyone's life, either directly or indirectly. Approximately 1 out of 3 people living in the United States will develop cancer at some point in their lifetimes (ACS 2020a). Globally, cancer is the second leading cause of death; an estimated 9.6 million cancer deaths and over 18.1 million cases occurred in 2018 (WHO 2018a,b). The incidences and mortality rates for specific types of cancers vary because of differences in economic development, age structure, and lifestyle or risk factors. Mortality rates often are higher for types of cancer related to poverty. As poorer countries undergo socioeconomic development, global cancer rates are expected to increase, because of changing cancer risk factors, aging populations, and improved reporting. By 2040, over 27 million cases a year are predicted, with the global burden of cancer shifting from high-income to low- and middle-income counties (Bray *et al.* 2018, ACS 2020b).

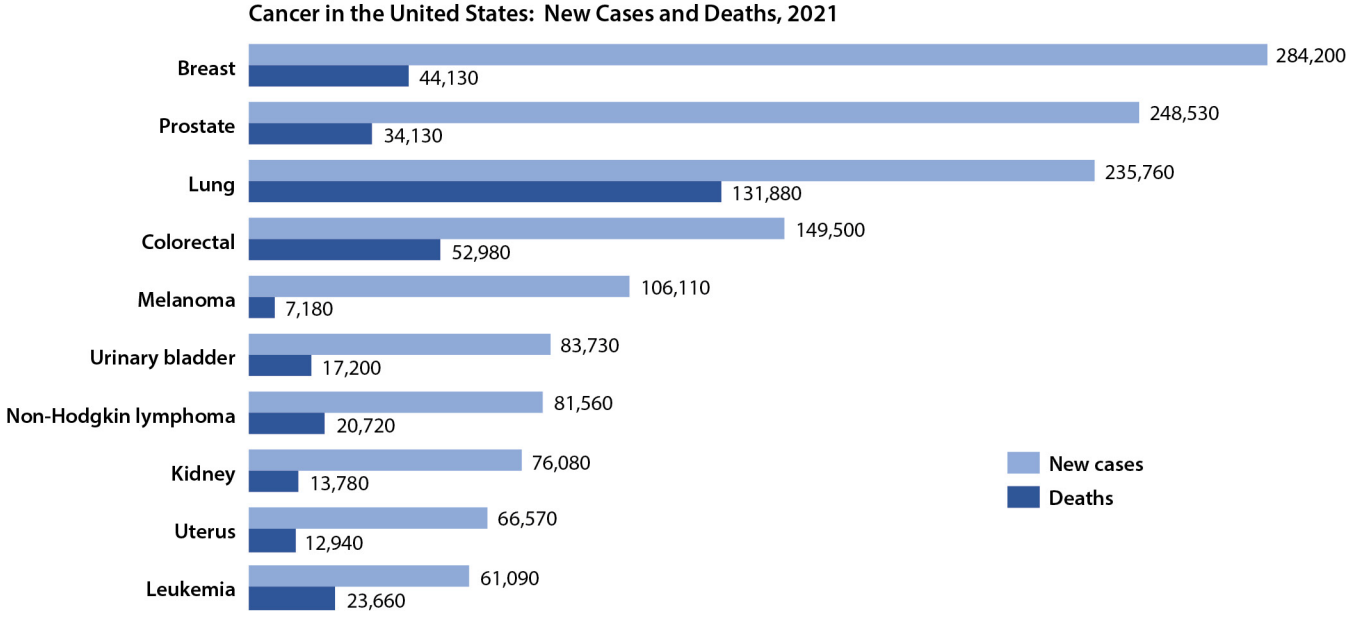
Cancer in the United States

Every day, 5,200 people are diagnosed with cancer and 1,670 die from cancer, translating to almost 1.9 million projected cancer cases and 608,570 cancer deaths for 2021. Cancer risk increases with age (up to age 74) and is most common among individuals aged 55 years or older (ACS 2021). Four types of cancer — breast (in women), lung, prostate, and colorectal cancer — account for over 60% of all cancer cases and over 70% of all cancer deaths. Other common types of cancer include melanoma of the skin, non-Hodgkin lymphoma, leukemia, and cancer of the urinary bladder, kidney, and uterus, as shown in the graph at the bottom of this page.

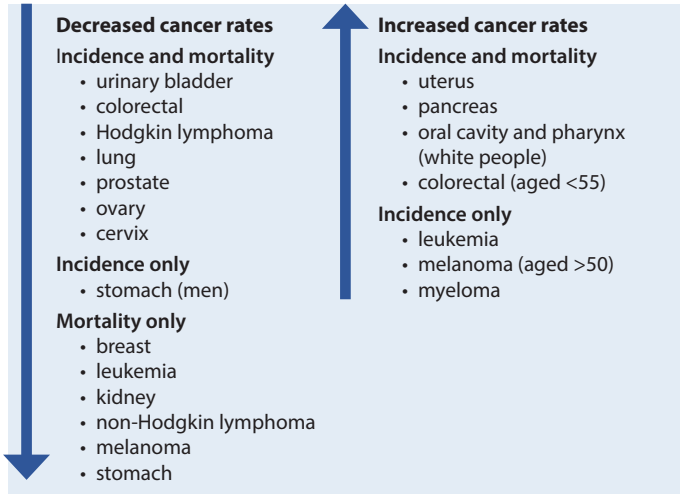
The good news is that overall cancer mortality (deaths per 100,000 population) has decreased by 29% since 1991 (ACS 2020a, Siegel *et al.* 2020). Both overall cancer incidence (new cases per 100,000 population) and mortality have decreased in the most recent decade for which data are available (ACS 2020a, Howlader *et al.* 2020). Notably, 2017 saw the largest decline in the death rate per year (2.2%) since 1992. The decreases in the rates of new cases and deaths are largely driven by long-term decreases in the four most common cancers (lung, colorectal, breast [deaths only], and prostate) and also reflect progress in prevention or treatment of several other types of cancers (as summarized in the box on the next page). After decades of steep increases, liver cancer incidence and mortality in men have stabilized in recent years (Howlader *et al.* 2020). But the incidences or death rates for other types of cancer have been increasing overall or in certain demographic groups. For example, colorectal cancer mortality and incidence have decreased among people over 55 but increased among those under 55.

The majority of people (67%) diagnosed with cancer at any tissue site are still alive five years after diagnosis, and survival rates for most types of cancer have improved since the mid 1970s. Survival rates are at least 90% for prostate cancer, melanoma of the skin, testicular cancer, thyroid cancer, and breast cancer (in women), but about 20% or less for cancer of the pancreas, liver, lung, and esophagus (ACS 2020a).

Although cancer affects all people, certain groups (primarily the poor and people of color) have a higher cancer burden. Of the major racial and ethnic groups, non-Hispanic black men have the highest cancer incidence and death rates (Siegel *et al.* 2020). Compared with non-Hispanic white people, non-Hispanic black people have higher death rates for the four most common types of cancer and death rates over twice as high for some other types of cancer, such as myeloma and cancer of the stomach, cervix, and uterus (ACS 2020a, Siegel *et al.* 2020). The disparities in death rates do not always reflect disparities in incidence. For example, breast cancer mortality is 40% higher among black women than white women despite similar incidence rates. For almost all types of cancer, survival rates are lower in black people than in white people, partly because cancer is diagnosed at later stages. Nevertheless, cancer stage at diagnosis does



Changes in Cancer Incidence and Death Rates — Last Decade*



*Incidence: 2007–2016; mortality: 2008–2017.

not completely explain racial and ethnic disparities; after adjusting for sex, age, and stage at diagnosis, the risk dying from cancer is 33% higher among black people and 55% higher among Alaska Natives than among white people (ACS 2020a, Siegel *et al.* 2020).

Cancer mortality disproportionally affects the poor in the United States and globally. Inequalities in wealth result in differences in exposure to environmental substances and other risk factors, such as chronic stress or underlying diseases that may make individuals more susceptible to developing cancer, and they pose barriers to high-quality prevention, early detection, and treatment (Siegel *et al.* 2018). In the United States, cancer incidence and death rates are highest among people of lower socioeconomic status. Among both black and non-Hispanic white men, those with less than 12 years of education are three times more likely than college-educated men to die of cancer (ACS 2020a).

Although deaths from childhood cancer have been decreasing since 1975, cancer remains the second leading cause of death among children in the United States. Approximately 1,190 children are expected to die of cancer in 2020 (ACS 2020a). Improvements in treatment are largely responsible for the decreasing death rate, and cancer incidence has been increasing in children (up to age 14) and in adolescents (aged 15 to 19) since 1975. In 2020, the number of newly diagnosed cancer cases is expected to exceed 11,000 in children and 5,800 in adolescents (ACS 2020a). The causes of childhood cancer are largely unknown; however, genetics and environmental exposure (including pre- and post-natal exposure) play important roles (Whitehead *et al.* 2016).

Children are particularly vulnerable to environmental risk factors, including numerous biological toxins and harmful exposures from air, food, water, medicines, pesticides, and ionizing radiation (Reuben 2010). The most common types of cancer observed in children are different from those in adults; children are more likely to develop cancer of the blood (primarily leukemia) and the brain and nervous system (central nervous system tumors and neuroblastoma, a tumor of the peripheral nervous system), a specific type of kidney cancer (Wilms tumor), and soft-tissue and bone tumors (ACS 2020a). The tumor profile for adolescents includes both childhood and adult cancers, and adolescents have a high burden of lymphoma (ACS 2020a, Siegel *et al.* 2020).

Beyond the toll on human life and health, cancer has a high economic cost. In 2015, the costs of cancer in the United States totaled $80.2 billion in direct medical costs (ACS 2018) and $94 billion in lost productivity due to premature death (Islami *et al.* 2019). In 2018, 27.5 million Americans did not have health insurance (U.S. Census Bureau 2019), and uninsured rates were highest among black and Hispanic people. These groups are more likely than white people to be diagnosed with cancer at later stages and to die of cancer (ACS 2020a). Lack of health insurance makes early detection of cancer and optimal treatment less likely.

Cancer Prevention

The World Health Organization (WHO) recognizes primary prevention as the most cost-effective and sustainable intervention for reducing the global burden of cancer (Jemal *et al.* 2014, Bray *et al.* 2015). The good news is that 42% of newly diagnosed cancers and 45% of cancer deaths in the United States are due to modifiable risk factors and can be prevented (ACS 2020a). The targets for primary prevention are environmental causes — including occupational exposures, pollution, household exposures, medical treatment, infections, exposures resulting from lifestyle choices, or naturally occurring exposures (such as to ultraviolet [UV] radiation in sunlight) (Reuben 2010, ACS 2020a). An important step in primary prevention is to identify the carcinogens. In 1978, the U.S. Congress passed legislation for this purpose, requiring the Secretary of Health and Human Services (HHS) to publish a report that identifies environmental causes of cancer. The National Toxicology Program (NTP) prepares the Report on Carcinogens for the Secretary, HHS.

What Listing in the RoC Means

A listing in the RoC identifies a substance or exposure circumstance as known or reasonably anticipated to be a human carcinogen and thus indicates a potential hazard. It does not estimate cancer risks to individuals associated with exposures in their daily lives, because many factors affect whether a person will or will not develop cancer, including the carcinogenic potency of the substance, the level and duration of exposure, and an individual's susceptibility to the carcinogenic action of the substance. Formal risk assessments are the responsibility of the appropriate federal, state, and local health regulatory and research agencies. The RoC does not attempt to rank the listed substances according to their potency. Finally, the report does not address any potential benefits of listed carcinogenic substances (such as chemotherapeutic agents for cancer patients).

How the RoC Addresses the Public Health Service Act

The box on the next page lists the four elements the congressionally mandated RoC is required to contain. This section describes how the RoC addresses the Public Health Service Act to (1) identify carcinogens, (2) estimate exposure, and (3) identify federal regulations to reduce exposure and cancer risk. The fourth type of information requested by Congress — to identify requests for carcinogenicity testing — is provided in Appendix E of the RoC, which includes a link to information on carcinogenicity testing activities at NTP. Specific information on each listed substance is provided in its substance profile, which discusses (1) the listing status, (2) cancer studies in humans and animals, studies of biologic mechanisms, and other data relevant to carcinogenicity, (3) the potential for human exposure in the United States, and (4) federal regulations to limit exposure.

Identifying Carcinogens

Studies in both humans and experimental animals are used to evaluate whether a substance potentially causes cancer in humans. The evaluation also considers other studies that may shed light on the potential carcinogen's possible mechanisms of action. The Handbook for Preparing Report on Carcinogens Monographs (NTP 2015) provides

Section 301(b)(4) of the Public Health Service Act, 42 USC 241(b)(4), as amended

The report should contain the following elements:

1. 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.
2. Information concerning the nature of such exposure and the estimated number of persons exposed to such substances.
3. 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.
4. 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.

guidelines on how to assess the studies and how to apply the listing criteria in order to reach a decision on listing a substance (see The Fifteenth RoC: Preparation and Contents, below). Each substance profile provides an overview of the studies that were considered key in the decision to list the substance in the RoC. Other organizations that evaluate substances for potential carcinogenicity include the WHO's International Agency for Research on Cancer (IARC), the Environmental Protection Agency of the State of California, and the U.S. Environmental Protection Agency (EPA); NTP uses their evaluations as a resource for identifying data on exposure and carcinogenicity.

The most applicable 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). Some of the first studies to identify carcinogens were occupational studies of workers exposed to high levels of carcinogens, including substances mined (e.g., asbestos) or extracted (e.g., benzene) from natural sources, synthesized chemicals (e.g., vinyl chloride), and complex mixtures (e.g., coal tar) (Fontham *et al.* 2009). Over time, the methods and quality of epidemiological studies have improved, with many studies emphasizing quantitative and semiquantitative data, evaluation of the impact of lower exposure levels, and exposure-response relationships (Loomis *et al.* 2017). In addition, epidemiological studies of patients receiving medical treatments (e.g., chemotherapeutic drugs or hormones), studies of lifestyle factors (such as alcohol consumption or tobacco smoking), and studies of environmental exposures or exposure circumstances in the general population contribute evidence for establishing a relationship between exposure and a particular type of cancer.

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 other factors, in addition to the exposure under study, that may affect cancer incidence (Rothman *et al.* 2012). The evaluation of human studies requires a critical analysis of the potential for biases and the ability of the study to detect a true effect. Several considerations — the strength of the association between exposure and cancer, consistency across studies, evidence of a relationship between the level or duration of the exposure and the risk of cancer (i.e., an exposure-response relationship), and the timing of exposure relative to the development of cancer (Hill 1965) — help guide the cancer evaluation (for more information, see the Handbook for Preparing Report on Carcinogens Monographs, NTP 2015). Nevertheless, despite some limitations, observational epidemiological studies have played a key role in identifying most of the substances listed in the RoC and by other authoritative bodies as known human carcinogens.

Another valuable method for identifying substances as potential human carcinogens is the long-term bioassay in experimental animals. Carcinogenicity testing in experimental animals began in the early 1900s, with studies showing that coal tar experimentally applied to the ears of rabbits caused malignant skin tumors, and has been used over the last four to five decades (as reviewed by Maronpot *et al.* 2004). Although animals are not perfect surrogates for humans, experimental evidence has demonstrated that rodents are similar enough to humans in their physiological, biochemical, metabolic, and genetic or genomic characteristics to warrant their use in predicting whether a substance is expected to cause cancer in humans. Moreover, all chemicals known to cause cancer in humans also cause cancer in experimental animals, and about a third of them were first identified in experimental animals (Huff 1993, 1999, Fung *et al.* 1995, Maronpot *et al.* 2004).

Data on the mechanisms of tumor formation are playing an increasingly important role in carcinogen hazard identification, because of the limited numbers of human and experimental animal studies. Moreover, mechanistic data can support the findings of cancer studies in humans and animals and increase confidence in these findings. For example, studies of the genetic makeup of tumor tissue have identified characteristic mutations ("mutational signatures") related to carcinogenicity for several substances listed in the RoC, which help to explain how UV radiation causes skin cancer, aflatoxin causes liver cancer, aristolochic acid causes cancer of the upper urinary tract, and vinyl chloride causes liver cancer (Stewart *et al.* 2016).

Several systematic frameworks have been proposed for evaluating mechanistic data in a cancer hazard assessment. The "hallmarks of cancer," proposed by Hanahan and Weinberg (2011), describe the biological capabilities that normal cells acquire during tumorigenesis, and can be used as a framework for evaluating mechanistic data (e.g., does a substance target a mechanism related to a cancer hallmark?). In contrast to evaluating mechanistic data by looking at the properties of cancer cells or tumors, Smith *et al.* (2016) proposed that the data be identified and organized according to characteristics of substances that are known to cause cancer. These "key characteristics of carcinogens" were identified from an evaluation of known human carcinogens by an IARC working group. They broadly include traits related to metabolism (transformation of substances into chemical products that can bind to and potentially damage DNA or other molecules) and traits related to adverse biological outcomes, such as causing effects (by various mechanisms) that lead to the accumulation of genetic damage in a cell, alter how genes are expressed (turned on or turned off), disrupt how cells or molecules communicate with each other, disrupt the immune system, and cause other effects resulting in uncontrolled growth of the damaged cells. No one carcinogen will have all of these traits, but most carcinogens will have at least one of them (Guyton *et al.* 2018). Another conceptual approach to evaluating mechanistic data is the "adverse outcome pathway" approach, which uses existing knowledge about the linkage between the molecular event that initiates tumor formation and the subsequent se-

ries of steps in tumorigenesis, spanning different levels of biological organization, that lead to an adverse outcome (Ankley *et al.* 2010).

In order to protect public health, demand is growing for cost- and time-efficient methods to prioritize substances for carcinogenicity testing, reduce the use of animals in testing, (as reviewed by Collins *et al.* 2008), and potentially predict carcinogenicity. Examples of these, provided in the table at the bottom of this page, include the federal interagency program Toxicology in the 21st Century (Tox21), EPA's Toxicity Forecaster, and EPA's Advancing the Next Generation of Risk Assessment (Next Gen) program (Cote *et al.* 2016, EPA 2016, NTP 2016b, Cogliano 2020). There are also growing initiatives to evaluate cancer hazards due to exposure to mixtures and classes of chemicals, rather than individual chemicals (ECHA 2020). Advances in exposure assessment methods and bioinformatics (the science of collecting and analyzing complex biological data) will facilitate the ability to measure the "exposome," which is a measure of an individual's total lifetime exposures to environmental agents (Cogliano 2020).

Estimating Exposure

The RoC is required to list only those substances to which a significant number of people living in the United States are exposed, and to provide information about the nature and extent of exposure 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, 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 resulting from environmental releases or occurrence, together with biomonitoring data (such as data from the National Health and Nutrition Examination Survey, CDC 2016), can be used to determine whether people in the United States are (or were) exposed to a substance. This information is included in each substance profile. Some substances whose use has been banned or restricted (e.g., safrole, arsenical pesticides, and mirex) are listed either because people who were previously exposed remain potentially at risk or because these substances are still present in the environment.

Providing Information on Reducing Exposure and Preventing Cancer

U.S. Federal Regulations and Guidelines To Reduce Exposure

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 substance profile a summary of the regulations and guidelines, if any, that are likely to decrease human exposure to that substance and thus are likely to reduce the risk of cancer and other adverse health effects. (Many of the regulations and guidelines set limits on exposure levels based on protection against adverse health effects other than cancer, but these limits may not be fully protective if cancer can be caused by exposures below the regulated levels.) The majority of these cited regulations are from the Consumer Product Safety Commission, U.S. EPA, U.S. Food and Drug Administration, and Occupational Safety and Health Administration (OSHA), and the primary guidelines are those published by the National Institute for Occupational Safety and Health (NIOSH) and the American Conference of Governmental Industrial Hygienists. Links to the websites 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.

Regulations Related To Listing in the RoC

Listing of a substance in the RoC may lead to enactment of additional federal or state regulations. Although the RoC is not a regulatory document, and government agencies are not required to take action when a substance is listed, certain federal and state regulatory agencies have chosen to base specific regulatory actions on the listing of a substance in the report. Both OSHA and the Mine Safety and Health Administration (MSHA) recognize the RoC as an authoritative source for identifying carcinogens for which hazard communications to workers are required (OSHA's Hazard Communication Standard and MSHA's Hazard Communication Standard). These communication requirements involve hazard labeling of shipped and workplace containers, preparation and distribution of safety data sheets to employees, and training of employees in the handling of known and suspected carcinogens. The State of California uses the RoC to identify carcinogens, which necessitates labeling requirements under the State's Safe Drinking Water and Toxic Enforcement Act (Proposition 65). Other states, such as Massachusetts and New Jersey, also use the RoC to identify substances for hazard communication to workers and the public or for the state's list of toxic substances (MDPH 2016, NJDPSOSH 2017, NJPHSB 2018).

In addition, the U.S. EPA uses the RoC as a source to identify carcinogens for the following regulatory purposes: (1) to prohibit ocean dumping of materials containing carcinogens (Criteria for the Evaluation of Permit Applications for Ocean Dumping of Materials under the Marine Protection, Research and Sanctuaries Act), (2) to report carcinogens above a *de minimis* concentration level for exporting purposes (Toxic Substances Control Act, Section 12[b], export notification requirements), and (3) to report carcinogens above a *de minimis* concentration level (0.1% of a mixture) to the Toxics Release Inventory (TRI). For some regulations, a listing in the RoC may directly trigger the regulation (e.g., ocean dumping) or a specific requirement under the regulation (e.g., export reporting), whereas for

Methods for Identifying Human Carcinogens

Epidemiology studies	Experimental animal studies	Mechanistic and related studies	Emerging mechanistic data
Occupational exposure General population: • Environmental exposures • Lifestyle exposures (e.g., tobacco smoking) • Exposure scenarios Patients receiving medical treatments (e.g., chemotherapeutic drugs)	Typically rodents Exposure to multiple doses for most of their lifetimes Doses: Relatively high but not toxic, chosen to increase the sensitivity of the assay, because a small number of animals are used to predict the effects in millions of people	Genomic data/mutational signatures Key characteristics of carcinogens: Biological effects common to many different carcinogens Hallmarks of cancer: Common traits by which a normal cell transforms to a cancer cell Adverse outcome pathway: Modeling of the sequence of molecular and cellular events that result in cancer following exposure to a carcinogen	High-throughput screening: • Tox21 • ToxCast *in vitro* assays NextGen approaches, including grouping chemicals, and "read-across" approaches, such as quantitative structure-activity relationship models

other regulations (e.g., the TRI), the listing may trigger an evaluation of the substance by the agency. Links to websites with information on the regulations mentioned above are provided at the end of this Introduction.

Reducing Exposure and Preventing Cancer Cases and Deaths

Primary prevention is a major rationale for current regulatory policies that aim to lower human exposure to cancer-causing substances and thereby improve public health by reducing the numbers of cancer cases and easing the economic burden of cancer. Regulations can also focus on other approaches to enhancing public health, such as providing medical benefits for those with cancer. Estimating the extent to which federal regulation of a substance listed in the RoC decreases exposure and protects public health is challenging, because little information is available on this topic. Since 1987, over 145 regulations from eight federal and six state agencies have cited the RoC (among other sources) in the *Federal Register* notice, federal supporting documentation, or state regulatory documents for regulatory action. As part of the risk-assessment process, some agencies conduct quantitative analyses that predict the numbers of cancer cases or deaths avoided and the associated cost savings due to decreased exposure resulting from the rulemaking. Over 70 federal regulations were determined to be "significant" as defined in Executive Order 12866.

An example of a successful program leading to decreased exposure to carcinogens in the United States is the Massachusetts Toxics Use Reduction Act (TURA) program (Jacobs *et al.* 2014). An analysis of exposure data for Massachusetts companies reporting to TURA during the period from 1991 to 2014 found that the use of carcinogens or suspected carcinogens, identified in the RoC and by other authoritative sources, declined by 32%, and reported releases declined by 93%.

In addition to quantitative risk assessment and regulations, the World Health Organization notes that qualitative cancer hazard identification (e.g., as a known or suspected carcinogen) can be a sufficient basis for action (for example, preventive measures and labeling to decrease tobacco-related cancers) (Cogliano 2020).

The importance of primary prevention is also demonstrated by several examples where decreasing exposure to carcinogens listed in the RoC and identified by other authoritative bodies has resulted in decreased cancer incidence or death rates, as summarized in the table at the bottom of this page.

The *Fifteenth Report on Carcinogens*: Preparation and Contents

Preparation and Listing Criteria

NTP prepares the RoC on behalf of the Secretary of Health and Human Services. To prepare the *Fifteenth Report on Carcinogens* (Fifteenth RoC), NTP followed a four-part process (described in detail in the next section, Process for Preparation of the RoC) using established listing criteria (see below). This process included input from the NTP Board of Scientific Counselors and the NTP Executive Committee, which includes the heads (or their designees) from several HHS agencies (FDA, National Cancer Institute, National Center for Environmental Health/Agency for Toxic Substances and Disease Registry, National Institute of Environmental Health Sciences, and NIOSH), as well as other federal agencies (Consumer Product Safety Commission, Department of Defense, EPA, and OSHA). The RoC monograph on each substance was prepared according to guidelines outlined in the protocols (methods) for each monograph, the RoC Handbook, or the introduction and methods sections of the monograph.

The criteria for listing an agent, substance, mixture, or exposure circumstance in the RoC are shown in the box on the next page. The listing criteria presented here were first adopted for use in the *Eighth Report on Carcinogens* (1998) and clarified the following year in two *Federal Register* notices (NTP 1999a,b). For more information, see History of the Report on Carcinogens (NTP 2016a). The listing criteria for substances listed in earlier editions of the RoC are outlined in the introductions to those editions.

Examples of Cancer Prevention

Exposure	Impact of cancer	Prevention measures	Decrease in cancer
Tobacco	Single most preventable cause of cancer; causes 80% of lung cancer cases in men and 40% in women worldwide[a]	Cancer prevention programs such as legislation, taxes on tobacco products, education[a]	Decrease in lung cancer mortality: 51% in men since 1990 and 26% in women since 2002[b] Mortality has decreased more slowly in women because smoking peaked 10 to 20 years later in women than in men[c]
Eight listed viruses	Contribute to 10% to 12% of all cancers[d]		
Hepatitis B virus	Causes 54% of liver cancer worldwide (~360,000 cases)[a,e]	Implementation of hepatitis B vaccination program in Taiwan[f]	80% decrease in liver cancer incidence in children and young adults[f]
Human papillomavirus	Responsible for all cervical cancer cases (570,000) and 120,000 cases of other types of cancer[e]	Vaccination in 80 countries	Elimination of cervical cancer as a public health concern is achievable this century via screening and vaccination programs[g]
Occupational	United States (2007): 20,386 cancer cases and deaths; medical cost $4.1 billion[h] Worldwide: 660,000 deaths; major cancer types are breast, lung, non-melanoma skin cancer, mesothelioma, and sinonasal cancer[i]	Workplace levels for some substances have been reduced in the United States since the 1970s[j,k]	Decreased incidences of specific occupation-related cancers[j]

Sources: [a]Thun *et al.* 2010, [b]ACS 2202a, [c]Weiss 1997, [d]Lunn *et al.* 2017, [e]Newton and de Martel 2020, [f]Bray *et al.* 2015, [g]Soerjomataram and Bray 2020, [h]Leigh 2011, [f]Espina *et al.* 2013, [i]Siemiatycki and Rushton 2020, [j]Espina *et al.* 2013, [k]Fontham *et al.* 2009.

Contents of the Fifteenth RoC

Listed Substances

Each edition of the RoC is cumulative and includes substances newly reviewed in addition to those listed in previous editions. Newly reviewed for this edition, the *Fifteenth Report on Carcinogens,* are eight substances (or classes of structurally related chemicals) (shown in the box below), including one bacterium and seven chemicals, bringing the total number of listed substances or classes of structurally related chemicals or agents to 256. These include 64 listings as *known to be a human carcinogen* and 192 listings as *reasonably anticipated to be a human carcinogen.* Six substances were reviewed but not listed in the Fifteenth RoC, including two haloacetic acids for which there were insufficient animal cancer data and two exposure circumstances that cause circadian disruption (persistent night shift work and certain lighting conditions, for which NTP cancer hazard assessments were published; see Appendix C).

A profile is written for each listed substance (as discussed under Identifying Carcinogens, above). For readers' convenience, profiles for related exposures, such as exposure to various types of UV radiation or to selected members of chemical families, such as nitroarenes, often are grouped together. New to the *Fifteenth Report on Carcinogens* is an additional grouping, Haloacetic Acids Found as Water Disinfection By-products (Selected).

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.

Substances Newly Reviewed for the Fifteenth RoC

Known to be a human carcinogen

Helicobacter pylori: chronic infection

Reasonably anticipated to be a human carcinogen

Antimony trioxide

Six haloacetic acids:

- Bromochloroacetic acid
- Bromodichloroacetic acid
- Chlorodibromoacetic acid
- Dibromoacetic acid
- Dichloroacetic acid
- Tribromoacetic acid

Supplemental Information

In addition to the substance profiles, the Fifteenth RoC contains the supplemental information identified in the table on the next page. As described in the following section of the RoC, Process for Preparation of the Report on Carcinogens, the Fifteenth RoC was prepared according to 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 NTP.*

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*For more information on the *Fifteenth Report on Carcinogens,* visit the NTP Office of the Report on Carcinogens website at the link provided at the end of this Introduction 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.

Supplemental information provided in the Fifteenth RoC

Section	Contents
Substances listed	Alphabetical list of substances listed in the RoC as *known to be a human carcinogen*
	Alphabetical list of substances listed as *reasonably anticipated to be a human carcinogen*
Glossary	Definitions of scientific and technical terms used in the substance profiles
Acronyms and abbreviations	Definitions of acronyms and abbreviations used in the substance profiles
Units of measurement	Definitions of units of measurement commonly used in the substance profiles
Appendix A	Cancer hazards not included in the RoC
Appendix B	List of agents, substances, mixtures, or exposure circumstances that have been delisted from the RoC
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Appendix D	List of participants who collaborated in preparation of the Fifteeenth RoC
Appendix E	Link to a searchable database of substances nominated to the NTP for toxicological testing
Appendix F	Cross-referenced list of listed substances and their common synonyms or abbreviations
Appendix G	List of Chemical Abstracts Service Registry Numbers of substances listed in the Fifteenth RoC

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Websites (Agencies and Regulations)

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 (IRIS)
  http://cfpub.epa.gov/ncea/iris/index.cfm
- Marine Protection, Research, and Sanctuaries Act
  Criteria for the Evaluation of Permits Applications for Ocean Dumping of Materials
  https://ecfr.io/Title-40/pt40.25.227#se40.27.227_16
- Toxic Substances Control Act (TSCA)
  TSCA Requirements for Exporting Chemicals
  https://www.epa.gov/tsca-import-export-requirements/tsca-requirements-exporting-chemicals
- Toxics Release Inventory Program
  https://www.epa.gov/toxics-release-inventory-tri-program

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

Mine Safety and Health Administration
https://www.msha.gov

- MSHA Hazard Communication
  http://arlweb.msha.gov/hazcom/hazcom.htm

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

Process for Preparation of the Report on Carcinogens
http://ntp.niehs.nih.gov/go/rocprocess

Handbook for Preparing Report on Carcinogens Monographs
http://ntp.niehs.nih.gov/pubhealth/roc/handbook/index.html

Scientific Reviews: Report on Carcinogens (RoC) Evaluations Since 1996
http://ntp.niehs.nih.gov/pubhealth/roc/listings/index.html

Occupational Safety and Health Administration (OSHA)
http://www.osha.gov

OSHA Hazard Communication Standard
https://www.osha.gov/dsg/hazcom/standards.html

State of California Safe Drinking Water and Toxic Enforcement Act
http://oehha.ca.gov/proposition-65/law/proposition-65-law-and-regulations