14th Report on Carcinogens

2016

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

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 box to the right lists the four elements the congressionally mandated RoC is required to contain.

The Burden of Cancer

Cancer — a group of diseases characterized by uncontrolled growth of abnormal cells that can result in death if not controlled — affects almost everyone's life, either directly or indirectly. About 1 out of 2 men and 1 out of 3 women living in the United States will develop cancer at some point in his or her lifetime (ACS 2016). Worldwide, over 14 million cases of cancer occur each year, and this figure is expected to reach nearly 22 million by 2030 (Bray *et al.* 2015). Cancer is the second leading cause of death globally, accounting for an estimated 8.2 million deaths in 2012 (Stewart *et al.* 2016). It disproportionately affects the poor, both in the United States and worldwide. Among both black and non-Hispanic white men in the United States, those with less than 12 years of education are three times more likely than college-educated men to die of cancer (ACS 2016). Of all cancer deaths worldwide, 70% occur in low- and middle-income countries. Moreover, the global burden of cancer is expected to increase in these poorer countries over the next two decades because of aging, population growth, and changes in cancer risk factors as these countries undergo economic transitions (Stewart *et al.* 2016). Beyond the toll on human life and health, cancer has a high economic cost. In 2009, cancer cost the United States over $243 billion, including $99 billion in medical costs, $19.6 billion in lost productivity due to illness, and $124.8 billion in lost productivity due to premature death (Reuben 2010).

Cancer Prevention

Reducing deaths from cancer will require not only improvements in treatment, but greater emphasis on cancer prevention and early detection (Stewart *et al.* 2016). The World Health Organization recognizes primary prevention as the most cost-effective and sustainable intervention for reducing the global burden of cancer (Jacobs *et al.* 2014). The good news is that over 35% of cancers are due to modifiable risk factors and can be prevented (Beaglehole *et al.* 2006, Reuben 2010, Stewart *et al.* 2016). The major causes of cancer are environmental factors, genetic factors, and physiological factors (e.g., related to hormones or immune conditions), and cancer may be caused by a combination of these factors occurring together or as a sequence of events. 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 2016). 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 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).

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

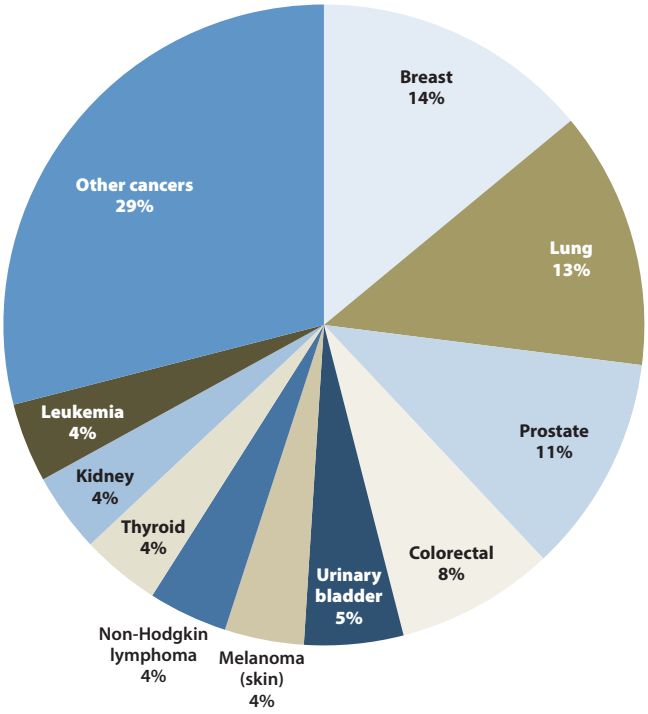
The report should contain the following elements:

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.

Cancer in the United States

In 2016, almost 1.7 million people living in the United States are expected to be diagnosed with cancer. An estimated 1,630 people will die from cancer each day, totaling over 590,000 projected deaths in 2016 (ACS 2016, Howlader *et al.* 2016). Most of these people (almost 70%) will develop one of ten different types of cancer, and the four most common cancers — breast, lung, prostate, and colon and rectal cancer — account for almost half of all new cases of cancer. The graph on the next page shows the ten most common types of cancer as percentages of all cancer projected for 2016.

Rates of cancer incidence (new cases) and mortality (deaths) vary with age, sex, race, and type of cancer. Most cancer (85%) is diagnosed in people aged 50 or older, and cancer rates are highest among black men and lowest among white women. The last ten years have seen decreases in total annual cancer incidence (by 1%) and mortality (by 1.5%) and in some of the most common cancers, such as lung cancer (incidence and mortality), prostate cancer (incidence and mortality), breast cancer (mortality), colorectal cancer (incidence and mortality), urinary-bladder cancer (incidence), and non-Hodgkin lymphoma (mortality). In contrast, the incidences of some cancers, such as anal cancer, kidney cancer, liver cancer, pancreatic cancer, melanoma, myeloma, and thyroid cancer, have increased (though the increases in



The ten most common cancers in the United States

kidney and thyroid cancer may be explained in part by improved methods for detecting these cancers). In addition, patterns in the incidence or mortality of specific types of cancer may vary by age, sex, or race. For example, increased rates have been seen for breast cancer among black women, colorectal cancer among people under the age of 50, leukemia among people over 50, and oral and pharyngeal cancer among white men (thought to be related to human papilloma virus) (ACS 2016, Howlader *et al.* 2016).

The majority of people (67%) diagnosed with cancer at any tissue site are still alive five years after diagnosis; however, relative five-year survival rates (survival of cancer patients compared with survival of healthy people of the same age, sex, and race) vary by cancer type (statistics for 2006 to 2012, Howlader *et al.* 2016). For example, survival is much lower for lung cancer (17.7%) than breast cancer (89.7%), which explains why there are more deaths from lung cancer although there are more new cases of breast cancer.

In contrast with trends in adults, the total incidence of cancer has been increasing in children (up to age 14), at a rate of 0.6% per year (ACS 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, even before birth (Reuben 2010). Although deaths from childhood cancer have been decreasing because of improved treatment and participation in clinical trials, cancer remains the second leading cause of death among children in the United States; the projected number of deaths for 2016 is 1,250 (ACS 2016). The causes of childhood cancer are largely unknown. The most common types of cancer observed in children are different from those in adults; children are more likely to develop cancers of the blood (leukemia), brain and central nervous system, and bone or soft tissue (Ward *et al.* 2014, ACS 2016).

How the RoC Addresses the Public Health Service Act

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 is potentially carcinogenic 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 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 Fourteenth 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 report. Other organizations that conduct evaluations of carcinogenicity include the World Health Organization'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); their evaluations serve as a resource to NTP for identifying exposure and carcinogenicity data.

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). Other epidemiological studies include those of patients receiving medical treatments (e.g., chemotherapeutic drugs or hormones), studies of lifestyle factors (such as alcohol consumption or tobacco smoking), or studies of environmental exposures in the general population.

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). 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) — are used to help guide the cancer evaluation (for more information, see the *RoC Handbook,* 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).

In addition to studies in humans and experimental animals, toxicological, toxicokinetic, and mechanistic studies can be used to identify carcinogens or provide evidence supporting the findings of cancer studies in humans and animals. For example, studies of the genetic makeup of tumor tissue have identified 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). Recently, Smith *et al.* (2016) proposed an approach for systematically evaluating mechanistic data by identifying and organizing the data according to ten biological effects that are caused by many different carcinogens. These ten 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 to metabolites that can bind and potentially damage DNA or other molecules — and those related to adverse biological outcomes, such as causing effects (by various mechanisms) that lead to the accumulation of genetic damage of 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 related to 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.

Testing methods that incorporate advances in molecular toxicology, computational sciences, and information technology also are being developed to prioritize substances for carcinogenicity testing and reduce the use of animals in testing (as reviewed by Collins *et al.* 2008). For example, the federal interagency program Toxicology in the 21st Century (Tox21, NTP 2016b) and EPA's Toxicity Forecaster (ToxCast, EPA 2016) both use high-throughput screening, in which automated methods can screen thousands of chemicals in a large number of assays to identify cellular processes that may predict toxicity. EPA's Advancing the Next Generation of Risk Assessment program (Next Gen) is also exploring approaches for evaluating and integrating mechanistic data or prioritizing chemicals. Examples of these approaches include using physical and chemical properties of molecules to predict their toxicity (structure-activity relationship modeling), analyzing large numbers of genes and their products measured in a biological sample (genomics, transcriptomics, and proteomics), conducting studies in cultured cells and short-term studies in experimental animals, using computational techniques for mining large amounts of data, employing methods for evaluating the relationship between expression of genes related to exposure and/or cancer (pathway and network analyses), and conducting clinical and molecular studies to measure key molecular changes in tissues from exposed humans (Cote *et al.* 2016).

The table at the bottom of this page summarizes the types of evidence streams being used to evaluate carcinogenicity.

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 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

Methods for Identifying Human Carcinogens

Epidemiology studies	Experimental animal studies	Mechanistic and related studies	Emerging mechanistic data
Occupational exposure	Typically rodents	Genomic data/ mutational signatures	High-throughput screening: • Tox21 • ToxCast *in vitro* assays
General population: • Environmental exposures • Lifestyle exposures (e.g., tobacco smoking)	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	Ten characteristics of carcinogens: Biological effects common to many different carcinogens	Studies of genetic mechanisms in whole organisms (e.g., zebrafish, roundworms) NextGen approaches
Patients receiving medical treatments (e.g., chemotherapeutic drugs)			

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, 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 on 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).

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 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 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

Estimating the extent to which listing a substance in the RoC or federal regulation of a substance listed in the RoC decreases exposure and protects public health is perhaps the most difficult task in preparing the RoC, because little information is available on this topic. An example of a successful program leading to decreased exposure to carcinogens in the United States is the Massachusetts Toxic 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%. Primary prevention is the rationale for current regulatory policies that aim to lower human exposure to cancer-causing substances and thereby improve public health. No studies were identified that evaluated the impact of specific federal regulations or a listing in the RoC on cancer incidence or mortality. Nevertheless, the importance of primary prevention is demonstrated by several examples where decreasing exposure to carcinogens listed in the RoC and identified by other authoritative bodies has resulted in decreased cancer mortality or morbidity, as summarized in the table below. In addition, studies have shown that federal regulations (e.g., EPA's Resource Conservation and Recovery Act, Clean Water Act, and Clean Air Act) have reduced exposure to a number of pollutants, resulting in decreased mortality, morbidity, and economic cost for diseases other than cancer (EPA 2010), which suggests that federal regulations also have the potential to reduce cancer risks.

The *Fourteenth 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 *Fourteenth Report on Carcinogens* (Fourteenth 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),

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: 38% in men and 12% in women since 1990[b] Mortality has decreased more slowly in women because smoking peaked 10 to 20 years later in women than in men[c]
Hepatitis B virus	Causes 54% of liver cancer worldwide[a]	Implementation of hepatitis B vaccination program in Taiwan[d]	80% decrease in liver cancer incidence in children and young adults[d]
Occupational	United States (2007): 20,386 cancer cases and deaths; medical cost $4.1 billion[e]	Workplace levels for some substances reduced in the United States since the 1970s[f,g]	Decreased incidences of specific occupation-related cancers[f]

Sources: [a]Thun *et al.* 2010, [b]ACS 2016, [c]Weiss 1997, [d]Bray *et al.* 2015, [e]Leigh 2011, [f]Espina *et al.* 2013, [g]Fontham *et al.* 2009.

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 (i.e., 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 below. 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.

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.

Contents of the Fourteenth 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 *Fourteenth Report on Carcinogens,* are seven substances (or classes of structurally related chemicals, shown in the box below), including five viruses, one metal-related class, and one chemical, bringing the total number of listed substances or classes of structurally related chemicals or agents to 248. These include 62 listings as *known to be a human carcinogen* and 186 listings as *reasonably anticipated to be a human carcinogen*.

Substances newly reviewed for the Fourteenth RoC

Known to be a human carcinogen

Epstein-Barr virus (EBV)
Human immunodeficiency virus type 1 (HIV-1)
Human T-cell lymphotropic virus type 1 (HTLV-1)
Kaposi sarcoma–associated herpesvirus (KSHV)
Merkel cell polyomavirus (MCV)
Trichloroethylene

Reasonably anticipated to be a human carcinogen

Cobalt and cobalt compounds that release cobalt ions *in vivo*

Trichloroethylene was first listed as *reasonably anticipated to be a human carcinogen* in 1999 and has been reclassified because of new studies finding sufficient evidence of carcinogenicity in humans. The new listing of Cobalt and Cobalt Compounds that Release Cobalt Ions *In Vivo* applies to a class of cobalt compounds and supersedes the previous listing of a specific cobalt compound, cobalt sulfate.

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, are often grouped together. New to the *Fourteenth Report on Carcinogens* are two additional groupings: (1) Viruses: Eight Listings, which includes the five newly reviewed viruses and three viruses or families of viruses that were previously listed in the RoC, and (2) Cobalt-Related Exposures, which includes the newly reviewed class of Cobalt and Cobalt Compounds That Release Cobalt Ions *In Vivo* and a previously listed substance, Cobalt–Tungsten Carbide: Powders and Hard Metals.

Supplemental Information

In addition to the substance profiles, the Fourteenth 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 *Fourteenth 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 the NTP.

Supplemental information provided in the Fourteenth 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	List of manufacturing processes, occupations, and exposure circumstances classified by IARC as carcinogenic to humans
Appendix B	List of agents, substances, mixtures, or exposure circumstances that have been delisted from the RoC
Appendix C	List of the agents, substances, mixtures, or exposure circumstances that have been reviewed but not recommended for listing in the RoC
Appendix D	List of participants who collaborated in preparation of the Fourteenth 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 Fourteenth RoC

References

ACS. 2016. *Cancer Facts & Figures 2016.* American Cancer Society. http://www.cancer.org/acs/groups/content/@research/documents/document/acspc-047079.pdf.

Beaglehole R, Bonita R, Magnusson R. 2011. Global cancer prevention: An important pathway to global health and development. *Pub Health* 125: 821-831.

Bray F, Jemal A, Torre LA, Forman D, Vineis P. 2015. Long-term realism and cost-effectiveness: Primary prevention in combatting cancer and associated inequalities worldwide. *J Natl Cancer Inst* 107(2): djv273. 8 pp.

CDC. 2016. National Health and Nutrition Examination Survey. Centers for Disease Control and Prevention. Last updated: 2/24/16. http://www.cdc.gov/nchs/nhanes.

Cote I, Andersen ME, Ankley GT, Barone S, Birnbaum LS, Boekelheide K, *et al.* 2016. The next generation of risk assessment multiyear study — Highlights of findings, applications to risk assessment and future directions. *Environ Health Perspect* [epub posted 4/19/16].

Collins FS, Gray GM, Bucher JR. 2008. Transforming environmental health protection. *Science* 319(5865): 906-907.

EPA. 2010. *Benefits and Costs of the Clean Air Act. Second Prospective Study, 1990 to 2020.* U.S. Environmental Protection Agency. Last updated: 4/15/10. http://www.epa.gov/air/sect812/prospective2.html.

EPA. 2016. *Toxicity Forecasting: Advancing the Next Generation of Chemical Evaluation*. The U.S. Environmental Protection Agency. Last updated: 3/4/16. https://www.epa.gov/chemical-research/toxicity-forecasting.

Espina C, Porta M, Schüz J, Hernández Aguado I, Percival RV, Dora C, *et al.* 2013. Environmental and occupational interventions for primary prevention of cancer: A cross-sectorial policy framework. *Environ Health Perspect* 121(4): 420-426.

Fontham ET, Thun MJ, Ward E, Balch AJ, Delancey JOL, Samet JM. 2009. American Cancer Society perspectives on environmental factors and cancer. *CA Cancer J Clin* 59(6): 343-351.

Fung VA, Barrett JC, Huff JE. 1995. The carcinogenesis bioassay in perspective: application in defining human cancer hazards. *Environ Health Perspect* 103(7-8): 680-683.

Hill, AB, 1965. The environment and disease; association or causation? *Proc R Soc Med* 58:295-300.

Hill, AB. 1971. *Principles of Medical Statistics,* 9th ed. New York: Oxford University Press.

Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, Altekruse SF, *et al.*, eds. 2016. *SEER Cancer Statistics Review, 1975-2013.* Surveillance, Epidemiology, and End Results Program, National Cancer Institute. http://seer.cancer.gov/csr/1975_2013.

Huff JE. 1993. Chemicals and cancer in humans: first evidence in experimental animals. *Environ Health Perspect* 100: 201-210.

Huff JE 1999. Value, validity, and historical development of carcinogenesis studies for predicting and confirming carcinogenic risks to humans. In *Carcinogenicity Testing, Predicting, and Interpreting Chemical Effects.* Kitchin KT, ed. New York: Marcel Dekker. pp. 21-123.

Jacobs MM, Massey RI, Tenney H, Harriman E. 2014. Reducing the use of carcinogens: The Massachusetts experience. *Rev Environ Health* 29(4): 319-340.

Leigh JP. 2011. Economic burden of occupational injury and illness in the United States. *Milbank Q* 89(4): 728-772.

Maronpot RR, Flake G, Huff J. 2004. Relevance of animal carcinogenesis findings to human cancer predictions and prevention. *Toxicol Pathol* 32(Suppl 1): 40-48.

NTP. 1999a. National Toxicology Program: Carcinogens Report, Tenth Edition — Substances, mixtures and exposure circumstances for listing or delisting. *Fed Regist* 64(63): 15983-15984.

NTP. 1999b. National Toxicology Program: Carcinogens Report, Tenth Edition — Substances, mixtures and exposure circumstances for listing or delisting. *Fed Regist* 64(74): 19188-19189.

NTP. 2015. *Handbook for Preparing Report on Carcinogens Monographs.* National Toxicology Program, Office of the Report on Carcinogens. http://ntp.niehs.nih.gov/pubhealth/roc/handbook/index.html.

NTP. 2016a. *History of the Report on Carcinogens (RoC).* The National Toxicology Program. Last updated: 7/12/16. http://ntp.niehs.nih.gov/pubhealth/roc/history/index.html.

NTP. 2016b. *Tox 21: Toxicology in the 21st Century.* The National Toxicology Program. Last updated: 3/21/16. http://ntp.niehs.nih.gov/results/tox21/index.html.

Reuben S. 2010. *Reducing Environmental Cancer Risk: What We Can Do Now.* 2008–2009 Annual Report of the President's Cancer Panel. National Cancer Institute. 240 pp. http://deainfo.nci.nih.gov/advisory/pcp/annualReports/pcp08-09rpt/PCP_Report_08-09_508.pdf.

Rothman KJ, Greenland S, Lash TL. 2012. *Modern Epidemiology.* Philadelphia: Lippincott Williams & Wilkins. 758 pp.

Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I, *et al.* 2016. Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis. *Environ Health Perspect* 124(6): 713-721.

Stewart BW, Bray F, Forman D, Ohgaki H, Straif K, Ullrich A, Wild CP. 2016. Cancer prevention as part of precision medicine: "Plenty to be done." *Carcinogenesis* 37(1): 2-9.

Thun MJ, DeLancey JO, Center MM, Jemal A, Ward EM. 2010. The global burden of cancer: Priorities for prevention. *Carcinogenesis* 31(1): 100-110.

Ward E, DeSantis C, Robbins A, Kohler B, Jemal A. 2014. Childhood and adolescent cancer statistics, 2014. *CA Cancer J Clin* 64: 83-103.

Weiss W. 1997. Cigarette smoking and lung cancer trends. A light at the end of the tunnel? *Chest* 111:1414-1416.

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