Cancer Classification Systems

Table of Contents

Overview: Cancer Classification Systems

Three US agencies and one international agency have cancer classification systems for carcinogens. The following information summarizes the cancer classification systems used by

- the National Toxicology Program (NTP) within the U.S. Department of Health and Human Services (DHHS),
- the National Institute for Occupational Safety and Health (NIOSH) within the U.S. Department of Health and Human Services,
- the U.S. Environmental Protection Agency (EPA), and
- the International Agency for Research on Cancer (IARC).

Carcinogen Classification Designations by Agency

Table 1. Cancer Classification Designations by Agency

Organization	Carcinogen Classifications
NTP	Known to be carcinogenic to humans Reasonably anticipated to be carcinogenic to humans
EPA (2005 criteria)	Carcinogenic to humans -Likely to be carcinogenic to humans Suggestive evidence of carcinogenic potential Inadequate information to assess carcinogenic potential Not likely to be carcinogenic to humans
EPA (1986 criteria)	Group A (carcinogenic to humans) Groups B1 and B2 (probably carcinogenic to humans) Group C (possibly carcinogenic to humans) Group D (not classifiable as to human carcinogenicity Group E (evidence of non-carcinogenicity for humans
IARC	Group 1 (carcinogenic to humans) Group 2A (probably carcinogenic to humans) Group 2B (possibly carcinogenic to humans) Group 3 (Not classifiable as to its carcinogenicity to humans Group 4 (Probably not carcinogenic to humans)
NIOSH	Occupational chemical carcinogens

Note: EPA based its 1986 classifications on a "weight of evidence" approach; their 2005 updated guidelines classify chemicals based on a "weight-of-evidence" *narrative* that includes evidence, uncertainties, and key assumptions. EPA did not reclassify all chemicals using the 2005 criteria.

National Toxicology Program (NTP)

NTP publishes the Report on Carcinogens (RoC), a congressionally mandated listing of chemicals that are known to be human carcinogens or reasonably anticipated to be human carcinogens. The RoC is updated periodically, and NCEH/ATSDR has input into prioritization of chemicals at NTP.

NTP Carcinogen Classification Criteria

The NTP listing categories are: (1) Known to be a Human Carcinogen and (2) Reasonably Anticipated to be a Human Carcinogen [NTP 2021].

Known to be a 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 a 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.
- 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
    - in multiple species or at multiple tissue sites;
    - by multiple routes of exposure; or
    - to an unusual degree with regard to incidence, site, type of tumor, or age at onset.
- There is less than sufficient evidence of carcinogenicity in humans or laboratory animals, but the agent, substance, or mixture belongs to a well-defined, structurally related class of substances whose members are listed in a previous RoC 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.

*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.

NTP Procedures

NTP completes a hazard assessment of each chemical it evaluates. The hazard assessment evaluates relevant information on dose response, route of exposure, chemical structure, metabolism, toxicokinetics, sensitive subpopulations, genetic effects, or other data that relate to mode of action or factors that may be unique to a given chemical. NTP does not quantify the potential cancer risk. NTP classifies the chemical on the basis of a careful review and integration of the body of evidence.

Any person can nominate an agent for listing in the NTP RoC. Once an agent is nominated, NTP prepares a background document for peer review at a public meeting. Next, NTP prepares a chemical profile document that provides a detailed analysis of the published scientific evidence relating to the potential cancer effects of the chemical. On the basis of this comprehensive analysis, NTP recommends a listing.

The chemical profile and recommended listing are then circulated to an external scientific panel for peer review. The draft chemical profile and recommended listing are then revised on the basis of the peer review comments and made available for public comment. NTP revises the profile after consideration of those comments and submits the revised RoC to HHS for final review and approval.

These procedures comprise a thorough, systematic review of the literature and a careful integration of the body of evidence, followed by peer and public review.

Environmental Protection Agency

EPA Integrated Risk Information System

The EPA IRIS program conducts hazard analysis and quantitative risk assessments of chemicals. (See http://www.epa.gov/iris/) Other EPA program offices then rely on these assessments to implement the statutes they administer, and IRIS relies upon EPA cancer guidelines to assess cancer risks posed by chemicals.

EPA Carcinogen Classification Criteria

EPA adopted cancer guidelines in 1986 and revised those guidelines in 2005. When EPA published the 2005 guidelines, it did not reclassify all the chemicals classified under the 1986 EPA guidelines. For that reason, we explain both systems here (Tables 1 and 2).

1986 EPA Cancer Guidelines

Under the 1986 guidelines, EPA summarized the weight of evidence for a chemical's potential as a human carcinogen and placed the chemical (agent) into one of the five categories in Table 1.

2005 EPA Cancer Guidelines

The 2005 EPA guidelines recommend describing a chemical's human carcinogenic potential in a "weight-of-evidence narrative" that gives a summary of available evidence relevant to cancer (as well as uncertainties and key default assumptions used) and describes conditions associated with a chemical's hazard potential. These guidelines give preference to information reported in peer-reviewed scientific journals.

The 2005 guidelines rely on the five cancer classifications described in Table 2.

Table 2. 1986 Definitions of EPA carcinogen classifications

Carcinogen classification	Definition
Group A Carcinogenic to humans	Agents with adequate human data to demonstrate the causal association of the agent with human cancer (typically epidemiologic data)
Group B Probably carcinogenic to humans	Agents with sufficient evidence (that is indicative of a causal relationship) from animal bioassay data but with either • limited human evidence that is indicative of a possible causal relationship, but not exclusive of alternative explanations (Group B1) or • little or no human data (Group B2).
Group C Possibly carcinogenic to humans	Agents with limited animal evidence and little or no human data
Group D Not classifiable as to human carcinogenicity	Agents without adequate data either to support or refute human carcinogenicity
Group E Evidence of non-carcinogenicity for humans	Agents that show no evidence for carcinogenicity in at least two adequate animal tests in different species or in both adequate epidemiologic and animal studies

EPA Procedures

EPA develops a narrative describing the potential for a chemical's carcinogenicity, relying on a weight-of-evidence analysis that includes any limitations based on dose-rate or dependence on mode of action. EPA emphasizes understanding the mechanism by which a chemical causes cancer to determine whether the mode of action is relevant to humans. This understanding is based on animal findings, risks to sensitive populations or life stages (for which the EPA has issued supplemental guidance), and evaluation of risk assessment options.

The EPA IRIS Assessment Development Process provides formal steps for extensive scientific peer and public review [USEPA 2019]. EPA bolstered the opportunities for public comment and peer review in 2011 in response to comments from the National Academy of Sciences [NAS 2000].

These procedures comprise a thorough, systematic review of the literature and careful weighing of the evidence, followed by peer and public review.

Table 3. 2005 Definitions of EPA carcinogen classifications

Carcinogen classification	Definition
Carcinogenic to humans	Requires convincing epidemiologic evidence of a causal association between human exposure and cancer. In cases where a causal association is not evident, the descriptor can indicate "strong" evidence of an association in humans, along with extensive evidence of carcinogenicity in animals by a similar mode of action.
Likely to be carcinogenic to humans	Requires a plausible association between human exposure and cancer. Evidence can include data from animal experiments in more than one species, sex, strain, site, or exposure route, with or without evidence of carcinogenicity in humans. The effects of metabolites, tumor type, tumor onset, or rarity are considered.
Suggestive evidence of carcinogenic potential	Indicates concern that the chemical may be a potential human carcinogen, even though data for a stronger conclusion may be absent. Available data may include studies showing a small increase in tumor incidence; some studies with positive results and others with negative results; or studies for which power, design, or conduct limits the ability to draw a confident conclusion.
Inadequate information to assess carcinogenic potential	Indicates not enough available data to apply one of the other descriptors.
Not likely to be carcinogenic to humans	Considers available data robust enough to support the conclusion that the chemical is not likely to cause cancer in humans. When animal experiments show positive cancer results, strong evidence must show that the mode of action does not take place in humans.

International Agency for Research on Cancer (IARC)

The IARC is a unit within the World Health Organization (WHO) that serves as an international research agency on cancer. IARC established its cancer classification criteria system in 1971 and was among the earliest public health organizations to classify carcinogens.

IARC produces well respected "Monographs on the Evaluation of Carcinogenic Risks to Humans." These documents serve as the basis for IARC cancer classifications.

IARC Carcinogen Classification Criteria

https://monographs.iarc.fr/wp-content/uploads/2019/01/Preamble-2019.pdf

The IARC classification system includes the five categories in Table 4.

Table 3. Definitions of IARC carcinogen classifications

Carcinogen classification	Definition
Group 1 Carcinogenic to humans	Is based on sufficient evidence in humans; or if both strong evidence in exposed humans that the agent exhibits key characteristics of carcinogens and sufficient evidence of carcinogenicity in experimental animals.
Group 2A Probably carcinogenic to humans	Is based on at least two of the following evaluations, including at least one that involves either exposed humans or human cells or tissues: • Limited evidence of carcinogenicity in humans, • Sufficient evidence of carcinogenicity in experimental animals, • Strong evidence that the agent exhibits key characteristics of carcinogens. If there is inadequate evidence regarding carcinogenicity in humans, there should be strong evidence in human cells or tissues that the agent exhibits key characteristics of carcinogens. If there is limited evidence of carcinogenicity in humans, then the second individual evaluation may be from experimental systems.
Group 2B Possibly carcinogenic to humans	When only one of the following evaluations has been made: • Limited evidence of carcinogenicity in humans, • Sufficient evidence of carcinogenicity in experimental animals, • Strong evidence that the agent exhibits key characteristics of carcinogens.
Group 3 Not classifiable as to carcinogenicity to humans	Agents that do not fall into any other group, including when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans for one or more tumour sites in experimental animals, the remaining tumour sites do not support an evaluation of sufficient evidence in experimental animals, and other categories are not supported by data from studies in humans and mechanistic studies. An evaluation in Group 3 is not a determination of non-carcinogenicity or overall safety. It often means that the agent is of unknown carcinogenic potential and that there are significant gaps in research.

IARC Procedures

The overall evaluation of evidence of carcinogenicity considers three types of data: animal, human, and mechanistic. IARC's expert Working Group classifies the animal or human evidence as strong, sufficient, limited, or inadequate. IARC describes its approach as "evaluations of the strength of the evidence for carcinogenicity arising from human and experimental animal data. The strength of the mechanistic evidence is also characterized." IARC bases the initial categorization on the combined level of evidence from the animal or human data. Strong mechanistic data can provide evidence for raising or lowering the initial category.

The IARC review process includes procedures to select chemicals for an evaluation of their potential carcinogenicity [IARC 2019]. Teams of international experts conduct IARC assessments for selected chemicals. The IARC defines procedures and criteria for selecting Working Group members, invited specialists, representatives of national and international health agencies, and observers. Working Group members must have no conflicts of interest; however, individual specialists may have affiliations, constituencies, or research support that would represent a conflict of interest. The goal of IARC assessments is to reach a broad consensus among Working Group members regarding the carcinogenicity of agents under consideration. According to IARC, the tasks of Working Group members are to:

- ascertain that all appropriate data have been collected;
- select the data relevant for the evaluation on the basis of scientific merit;
- prepare accurate summaries of the data to enable the reader to follow the reasoning of the Working Group;
- evaluate the results of epidemiological and experimental studies on cancer;
- evaluate data relevant to the understanding of mechanisms of carcinogenesis; and
- make an overall evaluation of the carcinogenicity of the exposure to humans.

IARC makes a concerted effort to obtain international expertise and reflect a variety of scientific views and findings. IARC permits observers and representatives from national and international health organizations to attend working group meetings, and makes names and affiliations of all participants public.

National Institute for Occupational Safety and Health (NIOSH)

NIOSH was established in 1970 as a research within the U.S. Centers for Disease Control and Prevention which focus is worker safety and health. NIOSH also develops guidance for safe and healthy workplace, including such about occupational carcinogens. The NIOSH Chemical Carcinogen Policy (NIOSH CIB 68) provides guidance on how NIOSH assesses and addresses cancer risks.

NIOSH Procedures

NIOSH will determine whether a chemical is an occupational carcinogen by using one of the three following methods:

- Evaluation of chemical carcinogen hazard assessments developed by the U.S. Department of Health and Human Services (HHS) National Toxicology Program (NTP) ("Known to be human carcinogen" or "reasonably anticipated to be human carcinogen"); the U.S. Environmental Protection Agency Integrated Risk Information System (IRIS) ("Carcinogenic to humans", "likely to be carcinogenic to humans" or "suggestive evidence of carcinogenic potential", Group A, Group B1, Group B2, or Group C) and the World Health Organization International Agency for Research on Cancer (IARC) ("Group 1," "Group 2A," or "Group 2B").
- Nomination by NIOSH for classification by NTP; or
- Classification by NIOSH

NIOSH may perform its own chemical hazard assessment to determine if the chemical should be classified as an occupational carcinogen when the institute has determined that the chemical has the potential for worker exposure and:

- no prior carcinogen classification by NTP, EPA or IARC has been published or
- information in the occupational relevance evaluation indicates the need for reconsideration of the evidence underlying a published chemical carcinogen assessment.

When developing a new chemical carcinogen classification, NIOSH will use the criteria for carcinogenicity contained in the United Nations' Globally Harmonized System for Classification and Labelling of Chemicals (GHS) (UN 2011), as included in the Occupational Safety and Health Administration (OSHA) Hazard Communication Standard (29 CFR §1910.1200), and any interpretation of the GHS criteria issued by OSHA. If NIOSH determines that the evidence for a chemical corresponds to GHS class 1A, 1B, or 2 (Table 4), and the chemical is occupationally relevant, then the institute will designate the substance an "occupational carcinogen."

Table 4. Classification categories for carcinogenicity under GHS (UN 2011)

Carcinogen classification Category	Hazard statement
1A Known to have carcinogenic potential for humans (based on human evidence)	May cause cancer
1B Presumed to have carcinogenic potential for humans (based on demonstrated animal carcinogenicity)	May cause cancer
2 Suspected human carcinogens (based on limited evidence of human or animal carcinogenicity)	Suspected of causing cancer

https://www.osha.gov/dsg/hazcom/ghsguideoct05.pdf

References

[IARC] International Agency for Research on Cancer. IARC Monographs on the Identification of Carcinogenic Hazards to Humans: Preamble to the IARC monographs 2019. Lyon, France: World Health Organization, International Agency for Research on Cancer, 20019. Available from: https://monographs.iarc.fr/cards_page/preamble-monographs/.

[NAS] National Academies of Sciences, Engineering and Medicine. 2000. Strengthening Science at the U.S. Environmental Protection Agency: Research-Management and Peer-Review Practices. Available from: https://www.nap.edu/read/9882/.

[NTP] National Toxicology Program. 15th report on carcinogens. Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, 2021. Available from: https://ntp.niehs.nih.gov/whatwestudy/assessments/cancer/roc/index.html#toc1.

[UN] United Nations. 2011. Globally harmonized system of classification and labelling of chemicals (GHS), 4th edition. New York and Geneva: United Nations. Available from: https://www.unece.org/fileadmin/DAM/trans/danger/publi/ghs/ghs_rev04/English/ST-SG-AC10-30-Rev4e.pdf.

[USEPA] US Environmental Protection Agency. Basic information about the integrated risk information system. Washington, DC: USEPA, Accessed 2019. Available from: https://www.epa.gov/iris/basic-information-about-integrated-risk-information-system#history.