

NIOSH Chemical Carcinogen Policy

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Disease Control and Prevention
National Institute for Occupational Safety and Health



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NIOSH Chemical Carcinogen Policy

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Foreword

Occupational exposure to chemical carcinogens still presents risks to many in the workforce. The burden from exposure to occupational carcinogens on workers, their families, employers, and the nation is difficult to measure. Cases are missed and go unreported because of the length of time, often decades, between exposure to a carcinogen and resultant cancer and because cancers can also have non-occupational causes, making it difficult to determine causation in individual cases. To aid in the prevention of occupational cancer, the National Institute for Occupational Safety and Health (NIOSH) develops guidance to protect workers from adverse effects of occupational carcinogens. This effort has spanned more than 40 years. In this current document, the policy by which NIOSH classifies chemicals as carcinogens, identifies control levels, and addresses analytical feasibility is being updated because of advances in science and with the intent of providing transparent guidance on how NIOSH assesses and addresses cancer risks.

Underlying this policy is the recognition that there is no known safe level of exposure to a carcinogen, and therefore that reduction of worker exposure to chemical carcinogens as much as possible through elimination or substitution and engineering controls is the primary way to prevent occupational cancer. Accordingly, this policy no longer uses the term *recommended exposure limit (REL)* for chemical carcinogens; rather NIOSH will only recommend an initial starting point for control, called the Risk Management Limit for Carcinogens (RML-CA). For each chemical identified as a carcinogen, this level corresponds to the 95% lower confidence limit of the risk estimate of one excess cancer case in 10,000 workers in a 45-year working lifetime. Keeping exposures within the risk level of 1 in 10,000 is the minimum level of protection and striving for lower levels of exposure is recommended. When measurement of the occupational carcinogen at the RML-CA is not analytically feasible at the 1 in 10,000 risk estimate, NIOSH will set the RML-CA at the limit of quantification (LOQ) of the analytical method. In addition, NIOSH will continue to evaluate available information on existing engineering controls and also make that information available when publishing the RML-CA.

The foundation on which the NIOSH chemical carcinogen policy is built is cancer hazard classification. To avoid government duplication and to utilize transparent and systematic assessments, NIOSH will evaluate existing cancer hazard assessments completed by the U.S. Department of Health and Human Services (HHS) National Toxicology Program (NTP), the U.S. Environmental Protection Agency (EPA) Integrated Risk Information System (IRIS), and the World Health Organization International Agency for Research on Cancer (IARC).

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Executive Summary

Occupational cancer is a burden on workers and society. The National Institute for Occupational Safety and Health (NIOSH) has a long history of identifying occupational chemical carcinogens and recommending approaches to control them. To better clarify how it will address reducing exposures to occupational chemical carcinogens, NIOSH revised its 1995 Chemical Carcinogen Policy. This newly revised Chemical Carcinogen Policy governs how NIOSH classifies chemicals as occupational carcinogens, sets risk management limits for workers exposed to carcinogens, and incorporates information on the analytical limit of quantification (LOQ).

Chemical Carcinogen Classification

Under this policy, NIOSH authoritative publications relating to chemical carcinogens will evaluate existing cancer hazard assessments completed by the U.S. National Toxicology Program (NTP), the U.S. Environmental Protection Agency (EPA), and the International Agency for Research on Cancer (IARC), whenever possible. Reliance on these preexisting hazard assessments and cancer classifications will allow NIOSH to focus its resources on assessing occupational risks and recommending ways of reducing those risks.

NIOSH will determine whether a chemical under consideration for the development of an authoritative recommendation is an occupational carcinogen by using one of the three following methods: (1) evaluation of chemical carcinogen hazard assessments developed by the U.S. Department of Health and Human Services (HHS) National Toxicology Program (NTP), the U.S. Environmental Protection Agency (EPA) Integrated Risk Information System (IRIS), and/or the World Health Organization International Agency for Research on Cancer (IARC); (2) nomination by NIOSH for Classification by NTP; or (3) classification by NIOSH.

As part of its determination, NIOSH will review each chemical carcinogen hazard assessment, in conjunction with the information noted in the Chemical Carcinogen Policy's Industrial Usage and Hazard Assessment and Scientific Studies sections, to determine if the chemical meets the criteria of occupational relevance. Those chemicals that meet the relevance criteria will be designated "occupational carcinogens."

Risk Management Limit

Because there is no known safe level of exposure to occupational carcinogens, NIOSH will continue to recommend reduction of exposure to an occupational carcinogen according to the hierarchy of controls through elimination or substitution and implementation of engineering controls, if practical, and the use of administrative controls before use of personal protective equipment (PPE). When exposures to carcinogens cannot be eliminated, NIOSH will also (1) calculate a range of risk estimates, from 1 excess cancer case in 100 workers

to 1 excess cancer case in 1 million workers over a 45-year working lifetime when the data permit, and (2) set a risk management limit for carcinogens (RML-CA). When data permit NIOSH to complete a quantitative risk assessment (QRA), NIOSH will use the results of the QRA to perform both tasks.

NIOSH will no longer use the term *REL* for occupational carcinogens. Instead, NIOSH will use the term *risk management limit for a carcinogen* or RML-CA. This change in terminology from the REL acknowledges that there is no known safe level for exposure to carcinogens and the RML-CA is a reasonable starting place for controlling exposures. An RML-CA is the daily maximum 8-hour time-weighted average concentration of a carcinogen above which a worker should not be exposed.

NIOSH will set the RML-CA for an occupational carcinogen at the concentration corresponding to the 95% lower confidence limit of the 1 in 10,000 (10^{-4}) risk estimate when analytically possible to measure. Historically, NIOSH issued recommended exposure limits (RELs) for carcinogens based on an excess risk level of 1 in 1,000 (10^{-3}), while acknowledging that there is no known safe level of exposure to a carcinogen. This level of risk was recommended because it could be analytically measured and achieved in many workplaces. However, in the last 25 years, advances in exposure assessment, sensor and control technologies, containment, ventilation, risk management, and safety and health management systems have made it possible, in many cases, to control occupational chemical carcinogens to a lower exposure level. Therefore, in order to incrementally move toward a level of exposure to occupational chemical carcinogens that is closer to background, NIOSH will begin issuing recommendations for RML-CAs that would advise employers to take additional action to control chemical carcinogens when workplace exposures result in excess risks greater than 10^{-4} .

Analytical Feasibility and Engineering Achievability

The ability to measure chemicals in the workplace is an important consideration for both evaluating and controlling worker exposures. When measurement of the occupational carcinogen at the RML-CA is not analytically feasible at the 1 in 10,000 risk estimate, NIOSH will set the RML-CA at the limit of quantification (LOQ) of the analytical method for that occupational carcinogen. In addition, NIOSH will continue to evaluate available information on existing engineering controls and make that information available when publishing RML-CAs.

Peer Review and Public Comment

NIOSH will continue its policy of seeking public and stakeholder input on its comprehensive analyses and recommendations, submitting them to peer review, and then publishing an authoritative document containing the recommendations and all supporting analyses recommending practices to control worker exposures.

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Abbreviations

DART	Division of Applied Research and Technology, NIOSH
DSHEFS	Division of Surveillance, Hazard Evaluations and Field Studies, NIOSH
EID	Education and Information Division, NIOSH
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
GHS	Globally Harmonized System of Classification and Labelling of Chemicals
HELD	Health Effects Laboratory Division, NIOSH
HHS	U.S. Department of Health and Human Services
IARC	International Agency for Research on Cancer
IRIS	Integrated Risk Information System
LOQ	Limit of quantification
NIOSH	National Institute for Occupational Safety and Health
NRC	National Research Council
NTP	National Toxicology Program
OD	Office of the Director, NIOSH
OSHA	Occupational Safety and Health Administration
PEL	Permissible exposure limit
PPE	Personal protective equipment
QRA	Quantitative risk assessment
REL	Recommended exposure limit
RHD	Respiratory Health Division, NIOSH
RoC	Report on Carcinogens
RML-CA	Risk Management Limit for Carcinogens
USC	United States Code

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1 Introduction

Purpose and Scope

Occupational cancer is a burden on workers and society. The National Institute for Occupational Safety and Health (NIOSH) has a rich history of identifying occupational carcinogens and recommending approaches to control them. Although progress has been made, much work needs to be done. NIOSH developed this Chemical Carcinogen Policy because clear policies on how to classify chemicals as occupational carcinogens, set risk management limits for workers exposed to carcinogens, and incorporate information on the analytical limit of quantification (LOQ) leads to further progress in reducing the risk and occurrence of occupational cancer.

Since 1970 NIOSH has reviewed evidence on chemical carcinogenicity to support recommended exposure limits (RELs). Under the Occupational Safety and Health Act of 1970 and the Federal Mine Safety and Health Act of 1977, NIOSH is mandated to

“...develop criteria dealing with toxic materials and harmful physical agents and substances which will describe exposure levels that are safe for various periods of employment, including but not limited to exposure levels at which no employee will suffer impaired health or functional capacities or diminished life expectancy as a result of his work experience.”
[29 United States Code (USC) 669 (a)(3) and for mining, 30 USC 811 (a)(1) and 30 USC 811 (a)(6)(B)].

NIOSH does so by undertaking an independent analysis of the scientific evidence on a chemical's carcinogenicity, evaluating how and where the chemical may be used in the workplace, and quantitatively

estimating the risk to workers at various exposure levels. NIOSH seeks public comment on these comprehensive analyses and recommendations, submits them to peer review, and then publishes an authoritative document containing the recommendations and all supporting analyses. These documents, usually Current Intelligence Bulletins or Criteria Documents, take significant resources to prepare.

Three policies from NIOSH are updated in this document: (1) the *NIOSH Occupational Chemical Carcinogen Classification Policy*, (2) the *Carcinogen Risk Management Limit Policy*, and (3) the *Analytical Feasibility and Engineering Achievability Policy*. Together, these three policies are referred to as the NIOSH Carcinogen Policy. The goal is to simplify the process of assessing cancer risks so that the documents NIOSH produces are more useful for its stakeholders, timelier, and more consistent with those of other agencies that assess cancer risks.

In performing this policy review, NIOSH sought suggestions and information from a range of organizations and the public. NIOSH published a request for information and held a public meeting to discuss the issues in December 2011. Information and comments from the public were submitted to NIOSH Docket 240: Announcement of Carcinogen and Recommended Exposure Limit (REL) Policy Assessment. NIOSH carefully considered this information and then prepared an initial draft Current Intelligence Bulletin, “Update of NIOSH Carcinogen Classification and Target Risk Level Policy for Chemical Hazards in the Workplace.” NIOSH again held a public meeting in December 2013 and sought comments from stakeholders and the public. Comments were submitted to NIOSH Docket 240A. NIOSH also solicited input from peer reviewers (see <http://www.cdc.gov/niosh/review/peer/HISA/carcinogen-pr.html>).

NIOSH carefully considered this critical information in revising its policies on (1) classifying chemicals as occupational carcinogens, (2) setting risk management limits for occupational carcinogens, and (3) incorporating information about the analytical LOQ for chemical carcinogens in the workplace. This document announces and explains these revised policies.

The science of risk assessment and carcinogenicity research is rapidly advancing. The policies described in this document are intended to provide transparent guidance on how NIOSH assesses cancer risks. They are not intended to constrain agency judgement such that strict adherence leads to assessments that do not represent current scientific thinking or assessments that are not suitable for the range of factors considered when assessing an individual chemical hazard. NIOSH will note and explain any variations in its practices when assessing cancer risks. NIOSH will also continue to engage scientific peers, stakeholders, and the public in the development and review of its assessments. NIOSH expects to update these policies as new science or agency experience indicates that these policies may have become outdated.

History of NIOSH Carcinogen Classification and REL Setting

To understand the changes that NIOSH is making to the policy for classifying chemical carcinogens, it helps to know the history of NIOSH efforts to classify workplace carcinogens.

1975: First NIOSH Carcinogen Policy

NIOSH first presented its carcinogen classification guidelines at the Conference on Occupational Carcinogenesis organized by the New York Academy of Sciences [Fairchild 1976]. The NIOSH guidelines recommended “no detectable exposure levels for proven carcinogenic substances.” Under

these guidelines, NIOSH classified a chemical as a carcinogen in two ways:

1. Any substance which is shown conclusively to cause tumors in animals should be considered carcinogenic and therefore a potential cancer hazard to man.
2. All tumorigens must be regarded as potential carcinogens, i.e., agents which produce benign tumors should be considered to be capable of producing malignant tumors.

The 1975 NIOSH cancer guidelines, were premised on the then-dominant assumption that it was not scientifically possible to predict safe levels of exposure to carcinogens. The NIOSH approach was consistent with that of the Occupational Safety and Health Administration (OSHA) and other national and international agencies at that time. For example, the 1958 Delaney Clause, an amendment to the 1938 Food, Drug and Cosmetic Act, stated that “the Secretary of the Food and Drug Administration [FDA] shall not approve for use in food any chemical additive found to induce cancer in man, or, after tests, found to induce cancer in animals.” FDA interpreted the Delaney Clause as requiring it to ban the use as a food additive of any substance shown to cause cancer in animals. Scientists voiced strong support for extending the Delaney Clause principles more broadly to environmental and occupational carcinogens [Fairchild 1976].

OSHA Cancer Policy

In 1977, OSHA published a Proposed Rule on the Identification, Classification, and Regulation of Toxic Substances Posing a Potential Occupational Carcinogenic Risk (“OSHA Cancer Policy”) [42 Fed. Reg. 54148]. OSHA faced the task of regulating many potential occupational carcinogens. In each rulemaking, many similar questions arose about how to identify and classify carcinogens and how much evidence of cancer-causing potential was needed to support OSHA regulation. The proposed OSHA Cancer Policy was designed to provide

a consistent framework for addressing these recurring issues. The proposed OSHA Cancer Policy defined a “potential occupational carcinogen” as

“...any substance or combination or mixture of substances, which causes an increased incidence of benign and/or malignant neoplasms, or a substantial decrease in the latency period between exposure and onset of neoplasms in humans or in one or more experimental mammalian species as the result of any oral, respiratory, or dermal exposure, or any other exposure which results in the induction of tumors at a site other than the site of administration. This definition also includes any substance that is metabolized into one or more potential carcinogens by mammals” [29 CFR 1990.103].

OSHA published the final Cancer Policy on January 22, 1980. The Cancer Policy created two classes of potential occupational carcinogens: Category I Potential Occupational Carcinogens were those with evidence of cancer-causing potential in humans or in animal tests that had been confirmed in another species, and Category II Potential Occupational Carcinogens were those for which the evidence of cancer-causing potential was “suggestive” [29 CFR 1990.112]. The Cancer Policy provided that when OSHA initiated rulemaking concerning a Category I Potential Occupational Carcinogen, the permissible exposure limit (PEL) should be set at the lowest feasible level [29 CFR 1990.142(a)(2)(iii)].

The requirement that OSHA set the PEL for Category I Potential Occupational Carcinogens at the lowest feasible level was short-lived. In July 1980, the Supreme Court issued an opinion in *American Petroleum Institute v. Industrial Union Department* [448 U.S. 607 (1980)] (commonly referred to as the *Benzene* decision). In *Benzene* the Supreme Court rejected the OSHA policy of automatically setting the PEL for a potential occupational carcinogen

at the lowest feasible level. Instead, the Supreme Court read section 3(8) of the OSH Act, 29 U.S.C. 653(8), the section which defines an occupational safety and health standard, to require that OSHA find “as a threshold matter that the toxic substance in question poses a significant health risk in the workplace and that a new, lower standard is therefore ‘reasonably necessary and appropriate’ to provide safe” workplaces [448 US at 14–15].

In response to the *Benzene* decision, OSHA published revisions to its Cancer Policy that deleted those provisions which required that the Agency automatically set the PEL for a Category I potential occupational carcinogen at the lowest feasible level [46 Fed. Reg. 4889]. OSHA also noted that “most provisions of the cancer policy are not affected by the *Benzene* decision. These include scientific policies, priority setting, identification criteria and classification criteria.”

1978: NIOSH Adopts “Potential Occupational Carcinogen”

In its 1978 testimony on the proposed OSHA Cancer Policy, NIOSH expressed general support for the definition of “potential occupational carcinogen” but recommended the following categories for carcinogens [NIOSH 1978b]:

Category I: Probable (or Confirmed) Occupational Carcinogen

Category II: Suspect Occupational Carcinogen

Category III: Carcinogenic Evidence Inconclusive

NIOSH began using the term *potential occupational carcinogen* to describe the carcinogenic potential of chemicals in the workplace shortly after its testimony on the OSHA Cancer Policy, in the *Criteria for a Recommended Standard: Occupational Exposure to Glycidyl Ethers* [NIOSH 1978a]. Since 1978, NIOSH has continued to use the term *potential occupational carcinogen*, without distinguishing between carcinogen categories in many

NIOSH Criteria Documents, Current Intelligence Bulletins, and testimony in OSHA standard-setting hearings.

NIOSH has decided to continue its approach of using one label for classifying all known and suspected chemical carcinogens. Although NIOSH recognizes the value of a tiered system in carcinogen classification for hazard communication, in practice, once a chemical has been designated a potential occupational carcinogen, the NIOSH risk management guidance has been the same. Therefore, NIOSH has decided not to adopt another tiered system as, without changing the NIOSH recommended risk management approach, it would complicate and confuse the process of carcinogen classification.

Until 1995, NIOSH had also set RELs at the lowest feasible concentration for occupational chemical carcinogens. NIOSH summarized its policy as follows:

“When thresholds for carcinogens that would protect 100% of the population had not been identified, NIOSH usually recommended that occupational exposures to carcinogens be limited to the lowest feasible concentration.” [NIOSH Pocket Guide to Chemical Hazards (Appendix A) [NIOSH 2007].

In testimony to OSHA in 1988 for rulemaking on air contaminants, NIOSH used the phrases “lowest feasible limit,” “lowest feasible level,” and “fullest extent feasible” interchangeably when describing how “potential occupational carcinogens” should be controlled in the workplace. NIOSH stated “... that work practices and engineering controls such as substitution, isolation, and ventilation should be used to control occupational exposures to the fullest extent feasible” [NIOSH 1988, p. 20]. Phrases such as “lowest feasible concentration” were recommended by NIOSH for controlling exposures to carcinogens until a change in policy occurred in 1995.

1995: NIOSH Projects Health Risks for Carcinogens

NIOSH revised its policy regarding exposure limits for carcinogens in 1995 to provide a more quantitative basis for RELs, including those for chemicals that were classified as potential occupational carcinogens:

“NIOSH recommended exposure limits (RELs) will be based on risk evaluation using human or animal health effects data, and on an assessment of what levels can be feasibly achieved by engineering controls and measured by analytical techniques. To the extent feasible, NIOSH will project not only a no-effect exposure, but also exposure levels at which there may be residual risks. This policy applies to all workplace hazards, including carcinogens...” [1995 policy cited in NIOSH 2007].

In accordance with this policy, most NIOSH RELs for carcinogens developed since 1995 have been based on (1) quantitative assessments of projected health risks at various exposure concentrations and (2) assessments of the feasibility of accurately measuring and controlling exposures to the hazard in the workplace [NIOSH 1995; NIOSH 2016; NIOSH 2013].

Since NIOSH revised its policy in 1995, NIOSH has most frequently recommended exposure limits for toxic chemicals, both those that are potentially carcinogenic and those that are not, at concentrations corresponding to an excess risk of 1 in 1,000 workers exposed to the substance for a 45-year working lifetime. The 1995 criteria document for coal mine dust discussed 1 in 1,000 as a risk level for chronic and serious respiratory health effects that did not involve cancer. Both the 2011 Current Intelligence Bulletin for titanium dioxide and the 2013 Criteria Document for hexavalent chromium compounds used 1 in 1,000 as the risk level for carcinogenic effects in setting RELs [NIOSH 1986, 1995, 2011a, 2013].

Under the 1995 policy, NIOSH also considered the “feasibility” of analytical methods [NIOSH 1994] in establishing RELs for some carcinogens. For example, the 1995 policy resulted in some RELs for

carcinogens being set at the LOQ of the analytical method, resulting in a higher REL than would have been established if based solely on an assessment of the health risk.

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2 Classifications of Chemical Carcinogens by NTP, EPA, and IARC

Under this newly revised policy, authoritative documents produced by NIOSH addressing chemicals thought to cause cancer will evaluate existing cancer hazard assessments completed by the U.S. National Toxicology Program (NTP), the U.S. Environmental Protection Agency (EPA), and the International Agency for Research on Cancer (IARC), whenever possible. Reliance on these pre-existing hazard assessments and cancer classifications will allow NIOSH to focus its resources on assessing occupational risks and recommending ways of reducing those risks.

The NIOSH proposal to use the hazard assessments already completed by NTP, EPA, and/or IARC found strong support in peer and public comments on the proposal. Commenters agreed that NIOSH reliance on hazard assessments completed by one of these agencies would increase NIOSH efficiency and allow it to focus its resources on estimating the magnitude of the risk a chemical poses to workers and recommendations for mitigating those risks.

Some industry commenters objected to NIOSH reliance on NTP, EPA, and or IARC hazard analyses, claiming that NIOSH should rely on a weight-of-evidence approach. Several commenters identified NTP consideration of the cancer causing potential of styrene as illustrative of the fact that NTP does not use a weight-of-evidence approach in classifying potential carcinogens. However, a thorough review conducted by the National Research Council (NRC) of the National Academy of Sciences found that the basis for the NTP cancer classification of styrene was sound [NRC 2014].

NIOSH believes carcinogen classification should employ a systematic methodology for critically

assessing and interpreting a body of scientific information. This methodology should include specific steps for the evaluation and integration of scientific information: defining a question or stating a problem of interest (causal question definition); creating a review protocol; identifying and selecting relevant information; evaluating individual studies (review of individual studies); assessing and integrating evidence across studies and providing an overall synthesis (data integration and evaluation); and interpretation of findings (drawing conclusions based on inferences) [Rhomberg et al, 2013]. These steps are important and are utilized by EPA, NTP, and IARC in their chemical carcinogen determinations. This type of review is critical for assessing and classifying chemical carcinogenicity. Whether this process is called “weight of evidence,” “strength of evidence,” “integration of evidence,” or “systematic review,” the important issue is that steps in the critical evaluation of chemical carcinogenicity should be made explicit [Weed 2005].

NTP, EPA, and IARC each describe their scientific approach as employing a thorough, systematic analysis of the body of evidence or evaluation of the strength of evidence using a transparent protocol and integration of evidence across studies. Each of these approaches for critically assessing and interpreting a body of scientific evidence satisfies NIOSH criteria.

For those chemicals that NIOSH is assessing, NIOSH will review the hazard assessment of chemicals with any of the cancer classifications listed in Table 2-1. Chemicals with classifications that fall within any of these categories will be treated similarly by NIOSH as it assesses the risk posed to workers.

Table 2-1. NTP, EPA, and IARC carcinogen classifications NIOSH considers when assessing occupational chemicals.

Organization	Carcinogen classification
NTP	Known to be carcinogenic to humans or reasonably anticipated to be carcinogenic to humans
EPA (2005 criteria)	Carcinogenic to humans, likely to be carcinogenic to humans or suggestive evidence of carcinogenic potential
EPA (1986 criteria)	Group A, Group B1, Group B2, or Group C
IARC	Group 1, Group 2A, or Group 2B

NIOSH views the assessments produced by NTP, IARC, and EPA to be of the highest scientific quality, subject to extensive peer review or prepared by acknowledged experts in the field in a consensus-building process. Below, NIOSH describes the key features of the cancer classifications of NTP, EPA, and IARC that give NIOSH confidence to rely upon them for its hazard assessment of occupational carcinogens.

National Toxicology Program

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. As of 2014, the RoC contains 243 listings and is updated periodically. NIOSH is a founding member of the NTP, has a representative on the NTP Executive Committee, has input into prioritization of chemicals at NTP, and has a vote in all procedural matters.

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 2016].

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

A chemical may be classified as reasonably anticipated to be a human carcinogen if any one of the following three circumstances apply,

- (1) 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,
- (2) 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
 - (i) in multiple species or at multiple tissue sites,

*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.

- (ii) by multiple routes of exposure, or
 - (iii) to an unusual degree with regard to incidence, site, type of tumor, or age at onset; or
- (3) 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.

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. On the basis of a careful review and integration of the body of evidence, NTP classifies the chemical.

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. These procedures are consistent with NIOSH requirements for hazard classification.

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 the EPA published the 2005 guidelines, it did not reclassify all the chemicals that had been classified under the 1986 EPA guidelines. For that reason, both systems are explained here (Tables 2-2 and 2-3).

1986 EPA Cancer Guidelines

Under the 1986 guidelines, EPA provided a summary of the weight of evidence regarding a chemical's potential as a human carcinogen and placed the chemical (agent) into one of the five categories in Table 2-2.

Table 2-2. 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 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

2005 EPA Cancer Guidelines

The 2005 EPA guidelines recommend a chemical's human carcinogenic potential be described 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. Preference is given to information reported in peer-reviewed scientific journals.

The 2005 guidelines rely on five cancer classifications as described in Table 2-3.

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 [EPA 2016]. EPA bolstered the opportunities for public comment and peer review in 2011 in response to comments from the National Academy of Sciences [EPA 2016].

These procedures comprise a thorough, systematic review of the literature and a careful weighing of the evidence, followed by peer and public review. These procedures are consistent with NIOSH requirements for hazard classification.

International Agency for Research on Cancer

IARC serves as an international research agency on cancer and is a unit within the World Health Organization. IARC established its cancer classification criteria system in 1971, and it was among the earliest organizations to classify carcinogens.

Table 2-3. 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, gender, 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 a 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 whose power, design, or conduct limits the ability to draw a confident conclusion.
Inadequate information to assess carcinogenic potential	Indicates there is not enough available data to apply one of the other descriptors.
Not likely to be carcinogenic to humans	Shows available data are considered 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.

The IARC adopted its most recent criteria in 2006. 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

The IARC classification system includes the five categories in Table 2-4.

Table 2-4. Definitions of IARC carcinogen classifications.

Carcinogen classification	Definition
Group 1 Carcinogenic to humans	Is based on sufficient evidence in humans; a causal relationship has been established between exposure to the agent and human cancer, or the animal evidence is sufficient, and there is strong mechanistic evidence in exposed humans that the agent or mixture acts through a carcinogenic mode of action relevant to humans.

(Continued)

Table 2-4 (Continued). Definitions of IARC carcinogen classifications.

Carcinogen classification	Definition
Group 2A Probably carcinogenic to humans	Indicates limited evidence in humans and sufficient evidence in animals. Alternatively, a chemical may be classified as Group 2A if there is inadequate evidence in humans but sufficient evidence in animals and strong evidence that the mechanism acts in humans.
Group 2B Possibly carcinogenic to humans	Indicates limited evidence in humans and less-than-sufficient evidence in animals; insufficient evidence in humans but sufficient evidence in animals; or animal evidence is limited, but there are other supporting data.
Group 3 Not classifiable as to carcinogenicity to humans	Is based on inadequate evidence in humans and inadequate or limited evidence in animals. This classification can also be made if there is sufficient evidence in animals and strong evidence that the mechanism does not act in humans.
Group 4 Probably not carcinogenic to humans	Is a rarely used category. A Group 4 chemical has strong and consistent evidence of lack of carcinogenicity in humans and animals.

IARC Procedures

The overall evaluation of evidence of carcinogenicity considers three types of data: animal, human, and mechanistic. The animal or human evidence is classified by the expert Working Group as sufficient, limited, inadequate, or suggesting lack of carcinogenicity. 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.” The initial category is based 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 [IARC 2006]. Teams of international experts conduct IARC assessments for each chemical. 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;

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; (ii) to select the data relevant for the evaluation on the basis of scientific merit; (iii) to prepare accurate summaries of the data to enable the reader to follow the reasoning of the Working Group; (iv) to evaluate the results of epidemiological and experimental studies on cancer; (v) to evaluate data relevant to the understanding of mechanisms of carcinogenesis; and (vi) to make an overall evaluation of the carcinogenicity of the exposure to humans.”

There is concerted effort by IARC to obtain international expertise and reflect a variety of scientific

views and findings. The Working Group meetings provide for the presence of observers and representatives from national and international health organizations. The names and affiliations of all participants are made public.

This systematic evaluation of all relevant data by recognized experts with consensus building on the carcinogen assessment are consistent with NIOSH requirements for hazard classification.

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3 Explanation of NIOSH Chemical Carcinogen Policy

NIOSH Occupational Chemical Carcinogen Classification Policy

NIOSH will determine whether a chemical under consideration for the development of an authoritative recommendation is an occupational carcinogen by using one of the three following methods: (1) evaluation of chemical carcinogen hazard assessments developed by the U.S. Department of Health and Human Services (HHS) National Toxicology Program (NTP), the U.S. Environmental Protection Agency (EPA) Integrated Risk Information System (IRIS), and/or the World Health Organization International Agency for Research on Cancer (IARC); (2) nomination by NIOSH for Classification by NTP; or (3) classification by NIOSH.[†]

Evaluation of NTP, EPA and IARC Carcinogen Classification Hazard Assessments

Review of Existing Carcinogen Classifications

NIOSH will initiate a review and evaluation of the occupational relevance of a chemical carcinogen that meets one or more of the designations in Table 3-1.

[†]The NIOSH Chemical Carcinogen Policy does not cover NIOSH evaluation of hazardous drugs. Hazardous drugs include those that exhibit one or more of the following six characteristics in humans or animals: (1) Carcinogenicity (2) Teratogenicity or other developmental toxicity (3) Reproductive toxicity (4) Organ toxicity at low doses (5) Genotoxicity or (6) Structure and toxicity profiles of new drugs that mimic existing drugs determined hazardous by the above criteria. NIOSH hazardous drug evaluation is consistent with the NIOSH Chemical Carcinogen Policy in that both include consideration of carcinogenicity and genotoxicity, both utilize information from IARC, NTP and EPA and both emphasize critically assessing and interpreting a body of scientific evidence. However, NIOSH evaluation of hazardous drugs is tailored to identify and evaluate data from human toxicity profiles, animal studies and in vitro studies unique to evaluating therapeutic agents. For example, NIOSH consults a variety of resources including but not limited to safety data sheets, product labeling approved by the U.S. Food and Drug Administration and databases such as DailyMed and DrugBank. For more information on NIOSH hazardous drug evaluation see “NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings,” <http://www.cdc.gov/niosh/index.htm>.

Table 3-1. NTP, EPA, and IARC carcinogen classifications NIOSH considers when assessing occupational chemicals.

Organization	Carcinogen classification
NTP	“Known to be human carcinogen” or “reasonably anticipated to be human carcinogen”
EPA 2005 criteria [*]	“Carcinogenic to humans, “likely to be carcinogenic to humans” or “suggestive evidence of carcinogenic potential”
EPA 1986 criteria [†]	Group A, Group B1, Group B2, or Group C
IARC [‡]	“Group 1,” “Group 2A,” or “Group 2B”

^{*}NIOSH will not review assessments developed by EPA using 2005 criteria that result in a finding of “inadequate information to assess carcinogenic potential” or “not likely to be carcinogenic to humans.”

[†]NIOSH will not review assessments developed by EPA using 1986 criteria that are included in Groups D or E.

[‡]NIOSH will not review assessments developed by IARC that are included in Group 3 or 4.

NIOSH reviews each chemical carcinogen hazard assessment, in conjunction with the information noted in the Industrial Usage and Hazard Assessment and Scientific Studies sections, to determine if the chemical meets the criteria of occupational relevance. By evaluating the hazard assessment of NTP, IARC, or EPA, NIOSH will increase the number of cancer assessments it can complete without sacrificing the scientific quality of those assessments. OSHA is also considering “ways to reduce the time and resources needed to independently evaluate the available study data by placing greater reliance on the efforts of other credible scientific organizations” [79 Fed. Reg. 61384].

Occupational Relevance Review

NIOSH will evaluate whether the chemical is likely to pose a risk in the occupational environment and whether the data underlying the cancer classification is applicable to the occupational setting. NIOSH will presume that a chemical classified as a carcinogen is occupationally relevant unless NIOSH finds convincing evidence that the chemical carcinogen is not relevant for the occupational exposure situation. This is because there are likely only very rare instances in which a chemical classified as a carcinogen by NTP, EPA, or IARC would not also be potentially carcinogenic to exposed workers. NIOSH will consider the issues described below in deciding whether a chemical is relevant to the occupational environment.

Industrial Usage Review

NIOSH will review if information from current industrial usage indicates the potential for worker exposure to the chemical. NIOSH will review each chemical carcinogen hazard assessment and any additional information on current chemical production and use, worker exposure data, and job descriptions where the chemical may be used, by means of peer-reviewed, published scientific studies, and other authoritative sources, including market analyses. Where such peer-reviewed literature is not available on chemical use and workplace exposures, NIOSH will rely upon other reliable research to determine whether a chemical poses a potential cancer threat to workers.

Typical workplace chemical exposures occur through inhalation or skin contact (although in special cases, oral exposures from hand-to-mouth routes or unique situations such as exposure through needle-stick injuries may be considered). Assessing the potential for worker exposure may in some cases identify ephemeral chemical intermediates that are produced only in closed systems. Workers are not likely to be routinely exposed to these intermediates in the workplace. However, NIOSH will also consider the potential for release into the work environment as the result of a spill or explosion.

In general, NIOSH will assume that inhalation and dermal studies are occupationally relevant because these are the typical exposures that workers encounter. NIOSH will also frequently consider studies with different routes of exposure, such as oral or injection studies, especially for carcinogens that act systemically. For example, animal studies in which exposure to the chemical is administered via drinking water, food, or intraperitoneal injection may provide relevant information about worker risks due to occupational exposure. Conversely, there may be cases where a chemical acts locally and only at an injection site. NIOSH may determine these types of studies do not establish that a chemical is occupationally relevant.

Hazard Assessment and Scientific Studies Review

NIOSH will review information and scientific studies relied upon by NTP, EPA, or IARC in developing each chemical carcinogen hazard assessment to determine (1) if the assessment is not relevant to occupational exposure or (2) if new information casts doubt on the scientific credibility of the assessment. Under such circumstances, NIOSH will either nominate the chemical to NTP for review or conduct a full review of the evidence and classify the chemical itself. This review will include consideration of route of exposure, tumor site, mode of action, and any other scientific information that may have bearing on the occupational relevance of the carcinogen classification.

NIOSH review may take place years after another entity completed its cancer hazard assessment and carcinogen classification. New studies may become available during the interim. NIOSH will consider whether the new studies would potentially change the overall evaluation. Such information may increase the concern for a carcinogen (for example, supporting an upgrade of a classification to “known to be carcinogenic to humans”). More infrequently, it may decrease the concern (for example, owing to new information showing that studies supporting a classification of “reasonably anticipated to be carcinogenic to humans” were conducted using a

substance containing a carcinogenic contaminant, casting doubt on the classification of the substance of interest). NIOSH will review evidence from any high quality, peer-reviewed, scientific study published after NTP, EPA, or IARC completed its hazard assessment (for example, an occupationally relevant scientific study published subsequent to the final record of studies contained in the underlying hazard assessment) to determine if the study suggests that the chemical no longer meets the criteria for the type of classification that NIOSH accepts for occupational relevance review. Under such circumstances, NIOSH will either nominate the chemical for NTP review or conduct a full evaluation of the information and classify the chemical itself.

Occupational Relevance Evaluation

NIOSH will determine whether the chemical is occupationally relevant and classify it as a NIOSH occupational carcinogen when there is a potential for worker exposure and the hazard assessments and scientific studies are applicable to occupational exposures. NIOSH will display the specific cancer classification each agency assigns to the chemical. NIOSH will also include the analysis in a NIOSH authoritative document describing the risks posed by the chemical in question.

Once NIOSH adopts the hazard assessment for a chemical, NIOSH will periodically review any revised NTP, EPA, and IARC hazard assessment and carcinogen classifications for that chemical and will update its determination as necessary to ensure the determination remains scientifically sound.

The 1995 NIOSH classification scheme did not distinguish between chemicals that are classified as carcinogens on the basis of multiple, occupational epidemiology studies, such as asbestos, benzene and cadmium, and those classifications that are based on extrapolations from animal bioassay data or other scientific information, such as titanium dioxide. NIOSH has been criticized because the 1995 policy does not allow for classifying chemicals on the basis of the magnitude and sufficiency of the scientific evidence.

Despite this criticism, NIOSH will continue to rely on a single cancer designation—that of occupational carcinogen. There are several reasons for this NIOSH decision. NIOSH has concluded that creating another cancer classification scheme, when several already exist, is unnecessary. NIOSH will evaluate classifications and analyses done by other entities. It will display the classification each entity has assigned to the chemical. What is important is the systematic evaluation of the scientific evidence of carcinogenicity that each entity relies upon to justify its classification. For chemicals that have been classified with certain designations, NIOSH will use the hazard assessment that supported the classification and review it to determine that it is comprehensive and up to date. NIOSH has determined it is unnecessary for it to duplicate these preexisting scientific analyses. Once NIOSH determines that a chemical is an occupational carcinogen, the cancer classification tier to which it is assigned has little relevance for NIOSH risk management recommendations. Therefore, the agency sees little to be gained by developing another tiered classification system.

The shift from a designation of “potential occupational carcinogen” to “occupational carcinogen” should not be interpreted as an effort by NIOSH to ignore the fact that the evidence of carcinogenicity for some chemicals is stronger than it is for other chemicals. For those chemicals that NIOSH is assessing, once sufficient evidence indicates that a chemical is reasonably expected to pose a cancer risk to workers, NIOSH will move forward to estimate the magnitude of that risk and make recommendations for reducing the risk and protecting workers from harm.

Nomination by NIOSH for Classification by NTP

NIOSH may nominate a chemical for review by NTP when NIOSH has determined that the chemical has the potential for worker exposure and (a) there is no prior carcinogen classification by NTP, EPA, or IARC or (b) information

in the occupational relevance evaluation indicates the need for reconsideration of the evidence.

Classification by NIOSH

If the chemical is of particular concern to NIOSH, NIOSH may develop its own hazard assessment of the chemical. NIOSH may perform its own chemical hazard assessment to determine if the chemical should be classified as an occupational carcinogen when NIOSH has determined that the chemical has the potential for worker exposure and (a) there is no prior carcinogen classification by NTP, EPA, or IARC or (b) 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 Labeling of Chemicals (GHS) that have been incorporated into the Occupational Safety and Health Administration (OSHA) Hazard Communication Standard 29 CFR §1910.1200 and any interpretation of the GHS criteria issued by OSHA. NIOSH will use the GHS criteria to assess carcinogenicity. If NIOSH determines that the evidence for a chemical corresponds to GHS class 1A, 1B, or 2, then NIOSH will designate the substance an "occupational carcinogen." Under the OSHA Hazard Communication Standard, manufacturers and employers may make reasonable chemical assessments that differ from those of government agencies, such as NIOSH and NTP. But for purposes of NIOSH carcinogen classification, NIOSH will rely on the GHS criteria as the basis of its risk management recommendations.

Chemical Carcinogen Risk Management Limit Policy

NIOSH will (1) determine a range of estimates from 1 excess cancer case in 100 workers to 1 excess cancer case in 1 million workers in a

45-year working lifetime when the data permit, and (2) set a risk management limit. Because there is no known safe level of exposure to occupational carcinogens, NIOSH will continue to recommend reduction of exposure to an occupational carcinogen as much as possible through substitution or engineering controls and administrative controls before use of personal protective equipment (PPE).

Determining a Range of Risk Estimates for Carcinogens

Quantitative Risk Assessment

After determining that a chemical is an occupational carcinogen, NIOSH will assess whether data are suitable for performing a quantitative risk assessment (QRA). If NIOSH determines that the data are suitable, NIOSH will perform a QRA based on the best available data.

The discussion below summarizes key elements of the NIOSH approach to QRA. NIOSH expects to publish more comprehensive guidance describing its approach to risk assessment in the future. Until then, NIOSH will continue to use the risk assessment methods as more fully described in the NIOSH Criteria Document on Hexavalent Chromium [NIOSH 2013] and Current Intelligence Bulletin on Titanium Dioxide [NIOSH 2011].

Evidence of Carcinogenicity

NIOSH bases its QRA on the best available data from human, animal, and/or mechanistic studies published in peer-reviewed scientific literature. The ideal data set for cancer risk estimation is an occupational epidemiology study with well-documented exposures, work histories, and health effects and many years of follow-up. However, other human studies, animal cancer bioassays, *in vitro* data, and mechanistic studies can all play a role in estimating risks of exposure. When conducting a QRA, NIOSH evaluates the data sets that are most pertinent to the exposure-response relationship and selects the data set(s) for analysis that can demonstrate a quantitative relationship.

Mathematical Models and Statistical Considerations

A QRA is used to estimate low-dose cancer risks by means of mathematical models to describe the exposure-response relationship. These statistical models project both a central estimate of the risk associated with occupational exposure and a statistically derived confidence interval for that estimate.

For carcinogen risk assessment, NIOSH generally treats exposure-response as low-dose linear unless a non-linear mode of action has been clearly established, in which case NIOSH will adopt a modeling approach defined by the data (including non-linear approaches when appropriate). In general, whether the model forms are linear or non-linear, any non-zero exposure to a carcinogen is expected to yield some excess risk of cancer.

When practical, given the available data for QRA, NIOSH will project both a central estimate and a 95% lower confidence limit estimate of various exposure concentrations of interest. NIOSH will base its risk estimates on the 95% lower confidence limit, when it is feasible to do so. The central estimate of risk is analogous to a mean or average concentration corresponding to a specific risk level, which in this example is 1 in 10,000. The 95% lower confidence limit is a measure of the imprecision in the risk estimate, and by using the 95% lower confidence limit as the basis for NIOSH risk estimates, there is greater assurance that workers are protected to at least a risk level of 1 in 10,000 over a working lifetime.

Mode of Action

The mode of action for carcinogens can affect the mathematical modeling assumptions and change the way a QRA is conducted. Genotoxic (“DNA-damaging”) carcinogens are presumed to act via non-threshold mechanisms, and occupational exposure limits for these chemicals are typically based on low-dose linear models.

It is often assumed that carcinogens that act through non-genotoxic mechanisms (such as hormonal

imbalance) or through indirect mechanisms (such as genotoxicity secondary to inflammation) may have response thresholds below which the carcinogenic mechanism is inoperative and the excess risk is zero. However, it has been noted that any supposed threshold for a carcinogen can be adequately modeled by a sublinear, but non-threshold, mathematical model. Because of this, it is highly unlikely that one can demonstrate empirically that a threshold exists [Crump 2011].

In practice, NIOSH has modeled the excess risk of cancer from a chemical believed to cause tumors in animals by a secondary genotoxic mechanism (for example, titanium dioxide), by fitting sub-linear but non-threshold models to the experimental data [NIOSH 2011]. In such a model, the excess risk of cancer is smaller at low doses than the risk that would be predicted by a linear model; however, some degree of excess risk is projected for any dose greater than zero. Therefore, like low-dose linear models, non-linear modeling approaches for non-genotoxic or indirectly genotoxic carcinogens imply that there will be some residual risk for any exposure greater than zero.

Sensitivity Analysis

The selection of final risk estimates upon which to base risk-management decisions depends on many factors in the QRA, including data source, biological relevance of the tumor site, modeling strategy, and biological plausibility of the model in the low-dose region, among many others. The best choice of a relevant and plausible set of options for risk assessment is not always evident. Therefore, NIOSH frequently conducts an analysis of plausible and relevant alternatives, called a sensitivity analysis which makes explicit the impact of specific risk assessment choices on the final risk estimates. In this type of analysis, one might see, for example, the impact of selecting the best-fitting plausible model, the most health-protective plausible model, or a weighted average of several models that are each individually plausible. The specific risk assessment choices that are analyzed are dependent upon the underlying risk assessment data and modeling

choices but provide transparency on the impact of alternative analytical choices on the estimated concentration of a chemical carcinogen that is anticipated to produce a 1 in 10,000 lifetime excess risk of cancer.

Range of Risk Estimates

NIOSH will utilize the QRA to determine a range of risk estimates including 1 excess cancer case in 100 workers, 1 excess cancer case in 1,000 workers, 1 excess cancer case in 10,000 workers, 1 excess cancer case in 100,000 workers, and 1 excess cancer case in 1 million workers. NIOSH will project both a central estimate and a 95% lower confidence limit estimate of the dose producing excess cancer risk, when the data are scientifically suitable for doing so.

Setting a Risk Management Limit for Carcinogens

Historically, NIOSH issued recommended exposure limits (RELs) for carcinogens based on an excess risk level of 1 in 1,000 in a working lifetime, while still acknowledging that there is no known safe level of exposure to a carcinogen. This level of risk was recommended because it could be measured and achieved in many workplaces. However, in the last 25 years, advances in exposure assessment, sensor and control technologies, containment, ventilation, risk management, and safety and health management systems have made it possible in many cases to control chemical carcinogens to a lower exposure level.

In keeping with these advances, NIOSH will set a “risk management limit for a carcinogen” or an “RML-CA,” at the concentration corresponding to the 95% lower confidence limit of the 1 in 10,000 risk estimate, but only when occupational measurement of the carcinogen at the RML-CA is analytically feasible. When measurement of the occupational carcinogen at the RML-CA is not analytically feasible at the 1 in 10,000 risk estimate, NIOSH will set the RML-CA at the limit of

quantification (LOQ) of the analytical method for that occupational carcinogen. NIOSH defines an RML-CA as the maximum 8-hour time-weighted average concentration of an occupational carcinogen above which a worker should not be exposed.

An excess lifetime risk level of 1 in 10,000 is considered to be a starting point for continually reducing exposures in order to reduce the remaining risk. NIOSH has established the terminology *RML-CA* instead of *REL* to bring the language used for NIOSH recommendations into conformity with the recognition that there is no known safe level of exposure to carcinogens. NIOSH will continue to recommend that employers reduce worker exposure to occupational carcinogens as much as possible through the hierarchy of controls, most importantly elimination or substitution of other chemicals that are known to be less hazardous, and engineering controls. Administrative controls, such as work practice controls, are also an important way to minimize workers’ exposures but are lower in the hierarchy. Personal protective equipment is the last line of defense, used when other methods do not adequately reduce exposures. Therefore, exposures should be kept *below* a risk level of 1 in 10,000, if practical.

Finally, several public commenters urged NIOSH to provide only the exposure limits that correspond to various risk levels, such as 1 in 1,000, 1 in 10,000, 1 in 100,000, or 1 in 1,000,000. Many of these commenters objected that NIOSH should not “recommend” one specific exposure level and should leave such a policy decision to OSHA. These commenters observed that NIOSH is a scientific research agency and that OSHA is the agency that is charged with making decisions about acceptable risks and feasibility. NIOSH agrees that it should provide information on the exposure levels that correspond to various levels of risk; however, NIOSH will continue to provide a health-based RML-CA to guide employers who seek to reduce exposures to occupational carcinogens to better protect their workers.

Analytical Feasibility and Engineering Achievability Policy

A sampling and analytical method that can accurately measure the exposure concentration over the recommended sampling period is necessary to assess occupational exposures below the RML-CA. NIOSH evaluates the method used to measure worker exposures to determine the LOQ, or how low a concentration can be reliably measured. It is important to identify a sampling and analytical method that can accurately measure the chemical at the health-based RML-CA (that is, the lower bound of the 1 in 10,000 excess cancer risk estimate), when it is available. After deriving the RML-CA, NIOSH will determine whether a NIOSH or OSHA analytical method can accurately measure the carcinogen at the RML-CA. If NIOSH determines that no partially or fully validated method is available, NIOSH will consider initiating research to develop a suitable method. When measurement of the occupational carcinogen is not analytically feasible at the lower bound of the 1 in 10,000 risk estimate, NIOSH will set the RML-CA at the LOQ of the analytical method for that occupational carcinogen.

Limit of Quantification

Several commenters criticized the NIOSH proposal to set the REL at the LOQ when the LOQ value is greater than the 1 in 1,000 cancer risk estimate presented in the public draft of this document. They urged that NIOSH should set the REL at the level necessary to protect worker health and not at some higher level. These commenters indicated that analytic methods change frequently, and a REL set at the LOQ will rapidly become out of date. Many of these commenters also suggested that NIOSH set two levels—the REL calculated to be health protective and the higher level suggested by the LOQ.

The ability to measure chemicals in the workplace is an important consideration for both evaluating and controlling worker exposures. When the LOQ is greater than the lower bound of the 1 in 10,000

risk estimate, NIOSH will consider initiating research to improve the LOQ for the analytical method. In addition, NIOSH will revise the RML-CA when the LOQ for a NIOSH or OSHA validated or partially validated analytical method is reduced.

Engineering Achievability

Section 6(b)(5) of the Occupational Safety and Health Act of 1970 (“Act”) requires OSHA to consider feasibility when setting occupational safety and health standards. Section 20(a)(3) of the Act directs NIOSH to recommend criteria for toxic substances that ensure that no employee suffers impaired health. Section 20 does not mention feasibility.

The science underlying the design and implementation of engineering controls is constantly advancing. Therefore, given the fast pace of rapidly changing engineering controls, NIOSH will not utilize the capability of controlling exposures (that is, engineering achievability) in setting RML-CAs. NIOSH will continue to recommend using a hierarchy of controls to reduce exposures to workers. NIOSH will continue to evaluate existing information on engineering controls and make that information available to the public.

Peer Review and Public Comment

Peer Review and Public Comment

NIOSH will continue its policy of seeking public and stakeholder input on its comprehensive analyses and recommendations, submitting them to peer review, and then publishing an authoritative document containing the recommendations and all supporting analyses recommending practices to control worker exposures. These documents are usually Current Intelligence Bulletins or Criteria Documents. NIOSH will seek peer review and public comment, consistent with the Office of Management and Budget's Information

Quality Guidelines,[§] about a determination regarding (1) chemical hazard assessment and occupational relevance reviews; (2) QRA for each occupational carcinogen, including but not limited to selection of data and mathematical models; (3) an-

[§]Office of Management and Budget. December 16, 2004. "Final Information Quality Bulletin for Peer Review." See http://www.whitehouse.gov/omb/memoranda_fy2005_m05-03

[§]Office of Management and Budget. "Final Bulletin for Agency Good Guidance Practices." January 18, 2007. See <http://www.whitehouse.gov/sites/default/files/omb/memoranda/fy2007/m07-07.pdf>

alytical methods for measuring the RML-CA; and (4) information regarding engineering controls.

Federal Register Notice

After considering all comments it receives, NIOSH will publish in the Federal Register a notice whether a chemical has been determined by NIOSH to be an occupational carcinogen, the reasons for the NIOSH classification, the RML-CA, and the range of risk estimates.

4 NIOSH Chemical Carcinogen Policy

Three policies from the National Institute for Occupational Safety and Health (NIOSH) are updated in this document: (1) the *NIOSH Occupational Chemical Carcinogen Classification Policy*; (2) the *Carcinogen Risk Management Limit Policy*; and (3) the *Analytical Feasibility and Engineering Achievability Policy*. Together, these three policies are referred to as the NIOSH Chemical Carcinogen Policy.

NIOSH Occupational Chemical Carcinogen Classification Policy

NIOSH will determine whether a chemical under consideration for the development of an authoritative recommendation is an occupational carcinogen, using one of the three following methods: (1) evaluation of chemical carcinogen hazard assessments developed by the U.S. Department of Health and Human Services (HHS) National Toxicology Program (NTP), the U.S. Environmental Protection Agency (EPA) Integrated Risk Information System (IRIS), and/or the World Health Organization International Agency for Research on Cancer (IARC); (2) nomination by NIOSH for Classification by NTP; or (3) classification by NIOSH.

Evaluation of NTP, EPA and IARC Hazard Assessments

Review of Existing Carcinogen Classifications

NIOSH will initiate a review and evaluation of the occupational relevance for a chemical carcinogen that meets one or more of the following designations:

1. NTP: “Known to be human carcinogen” or “reasonably anticipated to be human carcinogen;”
2. EPA (2005 criteria): “Carcinogenic to humans,” “likely to be carcinogenic to humans,” or “suggestive evidence of carcinogenic potential;”

Note: NIOSH will not review assessments developed by EPA using 2005 criteria that result in a finding of “*inadequate information to assess carcinogenic potential*” or “*not likely to be carcinogenic to humans*.”

3. EPA (1986 criteria): Group A, Group B1, Group B2, or Group C

Note: NIOSH will not review assessments developed by EPA using 1986 criteria that are included in Groups D or E.

4. IARC: “Group 1,” “Group 2A,” or “Group 2B.”

Note: NIOSH will not review assessments developed by IARC that are included in Groups 3 or 4.

Occupational Relevance Review

NIOSH reviews each chemical carcinogen hazard assessment, in conjunction with the information noted in the Industrial Usage and Hazard Assessment and Scientific Studies sections, to determine if the chemical meets the criteria of occupational relevance.

Industrial Usage Review

NIOSH will review if information from current industrial usage indicates the potential for worker exposure to the chemical.

NIOSH will review each chemical carcinogen hazard assessment and any additional information on current chemical production and use, worker exposure data, and job descriptions where the chemical may be used by means of peer-reviewed, published scientific studies, and other authoritative sources including, but not limited to, market analyses.

Hazard Assessment and Scientific Studies Review

NIOSH will review information and scientific studies relied upon by NTP, EPA, or IARC in developing each chemical carcinogen hazard assessment

to determine if the assessment is relevant to occupational exposure.

Note 1: During its evaluation of occupational relevance, if NIOSH finds a high quality, peer-reviewed, scientific study that casts doubt on the scientific credibility of the hazard assessment, then NIOSH will either nominate the chemical to NTP for review or conduct a full review of the evidence and classify the chemical itself.

Note 2: After NIOSH completes its evaluation of occupational relevance, if NIOSH finds a high quality, peer-reviewed, scientific study indicating that the chemical no longer meets the criteria for the type of classification that NIOSH accepts for occupational relevance review, then NIOSH will either nominate the chemical to NTP for review or conduct a full review of the evidence and classify the chemical itself.

Occupational Relevance Determination

NIOSH will determine whether the chemical is occupationally relevant and classify it as an occupational carcinogen when there is a potential for worker exposure and the hazard assessment and scientific studies are applicable to occupational exposures.

Nomination by NIOSH for Classification by NTP

NIOSH may nominate the chemical for review by NTP when NIOSH has determined that the chemical has the potential for worker exposure and (a) there is no prior carcinogen classification by NTP, EPA, or IARC, or (b) if information in the occupational relevance evaluation indicates the need for reconsideration of the evidence.

Classification by NIOSH

NIOSH may perform its own chemical hazard assessment to determine if the chemical should be classified as an occupational carcinogen when

NIOSH has determined that the chemical has the potential for worker exposure and (a) no prior carcinogen classification by NTP, EPA or IARC has been published or (b) 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), as included in the Occupational Safety and Health Administration (OSHA) Hazard Communication Standard.⁹

Chemical Carcinogen Risk Management Limit Policy

Because there is no known safe level of exposure to occupational carcinogens, NIOSH will continue to recommend reduction of exposure to an occupational carcinogen as much as possible through substitution or engineering controls, before use of personal protective equipment (PPE). When exposures to carcinogens cannot be eliminated, NIOSH will also (1) determine a range of risk estimates, from 1 excess cancer case in 100 workers to 1 excess cancer case in 1 million workers in a 45-year working lifetime, when the data permit, and (2) set a risk management limit.

Determining a Range of Risk Estimates for Carcinogens

Quantitative Risk Assessment

After determining that a chemical is an occupational carcinogen, NIOSH will assess whether data are suitable for performing a quantitative risk assessment (QRA). If NIOSH determines that the data are suitable, NIOSH will perform a QRA based on the best available data.

⁹29 C.F.R. 1910.1200 ("Hazard Communication").

Range of Risk Estimates

NIOSH will utilize the QRA to determine a range of risk estimates, including 1 excess cancer case in 100 workers, 1 excess cancer case in 1,000 workers, 1 excess cancer case in 10,000 workers, 1 excess cancer case in 100,000 workers, and 1 excess cancer case in 1 million workers. NIOSH will project both a central estimate and a 95% lower confidence limit estimate of the exposure producing excess cancer risk when the data are scientifically suitable for doing so.

Setting a Risk Management Limit for Carcinogens

NIOSH will no longer use the term recommended exposure limit (REL) for occupational carcinogens. Instead, NIOSH will use the term risk management limit for a carcinogen (RML-CA). An RML-CA is the maximum 8-hour time-weighted average concentration of a carcinogen to which a worker may be exposed.

Risk Management Limit

When data permit, and when measurement of the occupational carcinogen at the RML-CA is analytically feasible, NIOSH will set RML-CAs for occupational carcinogens at the concentration corresponding to the 95% lower confidence limit of the 1 in 10,000 risk estimate.

When data permit, but measurement of the occupational carcinogen at the lower confidence limit of the 1 in 10,000 risk estimate is not analytically feasible, NIOSH will set the RML-CA at the limit of quantification (LOQ) for the analytical method for that occupational carcinogen.

Analytical Feasibility and Engineering Achievability Policy

Analytical Feasibility

If NIOSH determines that there is no analytical method that is partially or fully validated that can

reliably measure the occupational carcinogen at the lower bound of the 1 in 10,000 risk level, NIOSH will consider initiating research to develop a suitable analytical method for the occupational carcinogen.

Engineering Achievability

NIOSH will continue to evaluate existing information on engineering controls and make that information available to the public.

Peer Review and Public Comment

Peer Review and Public Comment

NIOSH will seek peer review and public comment consistent with the Office of Management and Budget's Information Quality Guidelines^{**},^{††} about a determination regarding (1) chemical hazard assessment and occupational relevance reviews; (2) QRA for each occupational carcinogen, including selection of data and mathematical models; (3) analytical methods for measuring the RML-CA; and (4) information regarding engineering controls.

Federal Register Notice

After peer review and public comment, NIOSH will publish in the Federal Register a notice whether a chemical has been determined by NIOSH to be an occupational carcinogen, the reasons for the NIOSH classification, the RML-CA, and the range of risk estimates.

^{**}Office of Management and Budget. December 16, 2004. "Final Information Quality Bulletin for Peer Review. See http://www.whitehouse.gov/omb/memoranda_fy2005_m05-03

^{††}Office of Management and Budget. Final Bulletin for Agency Good Guidance Practices. January 18, 2007. See <http://www.whitehouse.gov/sites/default/files/omb/memoranda/fy2007/m07-07.pdf>

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