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Update of NIOSH Carcinogen Classification and Target Risk Level Policy for Chemical Hazards in the Workplace

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External Review Draft

Department of Health and Human Services
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National Institute for Occupational Safety and Health

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Executive Summary

The National Institute for Occupational Safety and Health (NIOSH) is the primary federal agency charged with conducting research and making recommendations for preventing occupational injuries, illnesses, and death, and it has unique expertise in assessing occupational risks. To improve workplace safety and lessen the health and economic impacts of cancer associated with work, NIOSH assesses workplace hazards posed by chemicals that may increase the risk of cancer. NIOSH uses carcinogen classifications from other research organizations and models the relationship between exposure to toxic and carcinogenic chemicals in the workplace and the adverse health effects associated with those exposures. The Institute evaluates the capacity of current technology to measure the level of exposure in a workplace, and recommends exposure limits to reduce the excess cancer risk associated with workplace exposures.

Scientific knowledge has advanced in recent years, and NIOSH stakeholders (those people, businesses, and organizations concerned with achieving healthy and safe workplaces) have offered suggestions about how to improve NIOSH policy that relates to workplace carcinogens. As a result, NIOSH is revising its policy for classifying chemical carcinogens and is making these changes to enhance the efficiency of assessing risk across the federal government, and to increase the relevance of information on workplace exposures to carcinogens.

Review of previous policy on carcinogens

A limitation identified in the previous policy was the term "potential occupational carcinogen," which dates to the 1978 NIOSH testimony on carcinogenic hazards [NIOSH 1978b]. The Occupational Safety and Health Administration (OSHA) also used the phrase in 1997 in the standard, "Identification, Classification, and Regulation of Carcinogens [29 CFR 1990.103]." In this phrase, the adjective "potential" conveys uncertainty that—given the current state of scientific knowledge of carcinogenicity—is not warranted with many carcinogens, such as asbestos, benzene, and cadmium.

In performing this policy review, NIOSH sought suggestions and information from a range of organizations and the public. This includes comments received during a public meeting on December 12, 2012, in Washington, D.C., and submissions provided to the NIOSH Cancer Policy Docket (Docket Number NIOSH-240). NIOSH carefully considered this critical information in revising chemical carcinogen classification and associated recommended exposure limit (REL) policies.

Policy changes

The new carcinogen classification policy (section 4) uses the hazard assessments made by the U.S. National Toxicology Program (NTP), the Environmental Protection Agency (EPA), and the

International Agency for Research on Cancer (IARC). NIOSH will evaluate the occupational relevance of these classifications to ensure that hazards are accurately identified and communicated in the occupational setting. Adopting the NTP, EPA, and IARC carcinogen classifications will make duplicated effort less likely. This will allow NIOSH to focus on evaluating the carcinogenic risk to workers and on developing workplace risk management recommendations, including recommended exposure limits (RELs).

If NIOSH finds the scientific basis of the carcinogen classification to be occupationally relevant, the chemical will be listed by NIOSH as an occupational carcinogen, along with the specific carcinogen classification listed by the NTP, EPA and/or IARC. NIOSH will also determine the applicable Globally Harmonized System for Classification and Labelling of Chemicals (GHS) carcinogen category (based on the GHS as adopted by OSHA in its 2012 revision of the OSHA Hazard Communication Standard [77 Fed. Reg. 17574-17896, 2012]). The NIOSH-assigned GHS carcinogen classification will improve risk communication for employers and workers by helping them identify hazards and then target strategies to reduce exposure.

This approach makes classification more efficient in federal and international organizations while giving unique information on workplace exposures. This will increase our ability to produce national recommended exposure limits.

Historically, NIOSH did not issue quantitative RELs for carcinogens. Rather, NIOSH recommended that exposures to chemical carcinogens be reduced to the lowest feasible level. This policy was amended in 1995 to project an array of exposure levels at which there may be quantified risks of cancer. However, a "target risk level" for such exposures was not established. Moving from a qualitative approach to a quantitative approach to risk assessment acknowledges excess risk, increases transparency for workers and employers, and it better relates to OSHA's work in developing occupational exposure limits.

Quantitative risk assessment

Whenever data quality permits, NIOSH derives risk-based recommended exposure limits by performing a quantitative risk assessment that uses the best available data. NIOSH uses the quantitative risk assessment to communicate an array of risk levels. These range from 1 cancer in 100 workers to 1 cancer in 1 million workers. NIOSH will set RELs to keep exposures below the 95% lower confidence limit estimate of the dose expected to produce 1 in 1,000 excess risk of cancer as a result of a 45-year working lifetime exposure (section 6). Although NIOSH recommends keeping occupational carcinogen exposures below the concentrations that produce a working lifetime risk of 1 in 1,000, this should be considered the minimum level of protection. Controlling exposures to lessen risk is always warranted. A risk near 1 in 1,000 is at least an order of magnitude higher than the cancer risk permitted in the United States for the general public.

NIOSH also evaluates the method used to measure worker exposures to determine the limit of quantitation, or how low a concentration can be reliably measured. If the limit of quantitation (or reliable quantitation limit) of the analytical method is higher than the REL, the REL will be set at the limit of quantitation (or reliable quantitation limit) of the analytical method. In this case, research will be considered to improve the sensitivity and accuracy of the method (section 6). NIOSH will designate these RELs with an analytical feasibility (AF) notation to alert users that these RELs have been established based on limitations of the sampling and analytical method (i.e., AF) and not at the "target risk level" of 1 in 1,000.

NIOSH RELs will be health-based and the Institute will no longer specifically consider technical achievability (i.e., ability to control exposures) in establishing RELs. Instead, recommendations will be provided that will note whether existing controls are available or effective, and this will include alternative risk management practices to reduce worker exposures.

NIOSH will publish all occupational carcinogen designations that it has assigned to GHS categories and RELs. This information will be listed in summary documents, such as the *NIOSH Pocket Guide to Chemical Hazards.*

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Contents

Acronyms

AF	analytical feasibility
DART	Division of Applied Research and Technology (NIOSH)
DHHS	Department of Health and Human Services
DRDS	Division of Respiratory Disease Studies (NIOSH)
DSHEFS	Division of Surveillance, Hazard Evaluations and Field Studies (NIOSH)
EID	Education and Information Division (NIOSH)
EPA	Environmental Protection Agency
GHS	Globally Harmonized System of Classification and Labelling of Chemicals
HELD	Health Effects Laboratory Division (NIOSH)
IARC	International Agency for Research on Cancer
ILO	International Labour Organization
IRIS	Integrated Risk Information System
LOD	limit of detection
LOQ	limit of quantitation
MSHA	Mine Safety and Health Administration
NIOSH	National Institute for Occupational Safety and Health
NTP	National Toxicology Program
OD	Office of the Director (NIOSH)
OECD	Organization for Economic Cooperation and Development
OSHA	Occupational Safety and Health Administration
QRA	quantitative risk assessment
REACH	Registration, Evaluation, Authorisation and restriction of Chemicals
REL	recommended exposure limit
RoC	Report on Carcinogens
RQL	reliable quantitation limit

1.0 Introduction

Occupational cancer is a burden on workers and society. NIOSH has a rich history of identifying occupational carcinogens and recommending ways to control them. Although progress has been made, much work needs to be done. Clear policies that protect workers will lead to further progress in reducing the risk and occurrence of occupational cancer.

Advancements in cancer science and NIOSH stakeholder concerns about limitations in the NIOSH approach to classifying and controlling carcinogens prompted this review of the NIOSH carcinogen classification policy. A major limitation identified is use of the term "potential occupational carcinogen," which dates to the 1978 NIOSH testimony on carcinogenic hazards. The phrase was also used by the Occupational Safety and Health Administration (OSHA) in its 1997 hazard classification for carcinogens outlined in 29 CFR 1990.103 (see section 2). The adjective "potential" conveys uncertainty that is not warranted with many carcinogens, such as asbestos, benzene, and cadmium [29 CFR 1990.103].

Further, the existing NIOSH carcinogen policy does not allow for classifying chemicals based on the magnitude and sufficiency of the scientific evidence. In contrast, other organizations—such as the National Toxicology Program (NTP), the Environmental Protection Agency (EPA), and the International Agency for Research on Cancer (IARC)—have differential classification systems with categories that reflect a systematic review of the scientific evidence [NTP 2011; EPA 2005; IARC 2006].

At the same time that NIOSH recognized this language limitation, occupational safety and health experts from around the world saw the need for more efficient and faster classification of chemicals and for considering alternatives that are less toxic and more environmentally sustainable [Schifano et al. 2011; EPA 2011a; Schifano 2011; American Chemistry Council 2011]. The approach outlined in this document will improve classification efficiency by using classifications from federal and international organizations. NIOSH will evaluate these classifications in light of information on workplace exposures. Implementing this process should lessen the time it takes to develop national recommended exposure limits, allowing for more chemicals to be assessed.

Once chemical carcinogens have been classified, quantitative risk assessments are typically conducted to characterize the risks of occupational exposure. Quantitative risk assessment serves as the health basis of recommended exposure limits (RELs). Because it can take large amounts of time and resources to assess risk and develop RELs, NIOSH is also investigating qualitative and semi-quantitative approaches, such as hazard banding, to address the vast number of unregulated chemicals.

In undertaking this carcinogen policy review, NIOSH sought input from a range of organizations and the public. This input is reflected in the carcinogen classification policy that follows. This policy document focuses on carcinogenic chemical hazards in the workplace.

2.0 NIOSH Carcinogen Classification History

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.

NIOSH presented its first carcinogen guidelines at the Conference on Occupational Carcinogenesis, organized by the New York Academy of Sciences in 1975 [Fairchild 1976]. The NIOSH guidelines recommended "no detectable exposure levels for proven carcinogenic substances." NIOSH described carcinogens 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.

This NIOSH policy, which considered that predicting safe levels of carcinogens was not scientifically possible, was consistent with conclusions of other national and international agencies at that time. The 1958 Delaney Clause, an amendment to the 1938 Food, Drug and Cosmetic Act, stated that "the Secretary of the Food and Drug Administration 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." Strong support was expressed for extending this legislation to other carcinogens, including occupational carcinogens [Fairchild 1976].

In 1977, OSHA published a Proposed Rule on the Identification, Classification and Regulation of Toxic Substances Posing a Potential Occupational Carcinogenic Risk (i.e., the OSHA Cancer Policy) [42 Fed Reg. 54148 (1977)]. It defined "potential occupational carcinogen" as the following:

> "... 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 occupational carcinogens by mammals (29 CFR 1990.103)."

In its 1978 testimony to the Department of Labor on the proposed OSHA Cancer Policy, NIOSH expressed general support for the definition of "potential occupational carcinogen," but it 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 has not consistently classified chemicals by using these carcinogen categories. NIOSH testimony in 1986 on formaldehyde stated that evidence "... indicate[s] that formaldehyde should be regarded as a Category I Potential Occupational Carcinogen" [NIOSH 1986]. In 1987 testimony on ionizing radiation, NIOSH stated that "Radon progeny should be considered a Category I 'potential occupational carcinogen'" [NIOSH 1987b]. However, the updated NIOSH criteria document for formaldehyde and the final criteria document for radon did not mention those categories and referred only to the designation "potential occupational carcinogen" [NIOSH 1981, NIOSH 1987a].

The first time NIOSH used the term "potential occupational carcinogen" in a document was in the NIOSH Criteria for a Recommended Standard: Occupational Exposure to Glycidyl Ethers [NIOSH 1978a]. Since then, this terminology has been reaffirmed in many NIOSH criteria documents and current intelligence bulletins, including the recent NIOSH Current Intelligence Bulletin 63: Occupational Exposure to Titanium Dioxide [NIOSH 2011a].

Although the term "potential occupational carcinogen" remained constant over the years, NIOSH policy on RELs for "potential occupational carcinogens" has evolved. The historical NIOSH REL policy was not intended to mean that "potential occupational carcinogens" should be banned in the workplace. Instead, the policy reflected more practical considerations. The historical REL policy is summarized in the *NIOSH Pocket Guide to Chemical Hazards* (Appendix A) [NIOSH 2007]:

> "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."

The "lowest feasible concentration" was not a quantitative value that NIOSH recommended. The intent was for employers at each workplace to determine this value, based on how the employer evaluated the available options that were technically and economically feasible.

This "lowest feasible concentration" policy for carcinogens was in place until 1995 [NIOSH, 1995b]. By that time, methods were available to conduct quantitative evaluations based on science and the occupational safety and health community realized that more quantitative guidance would

be useful. NIOSH policy was changed to give a more quantitative basis for RELs, including those for "potential occupational carcinogens":

> "NIOSH recommended exposure limits (RELs) will be based on risk evaluations 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].

Because of this policy, most RELs that NIOSH developed since 1995 were based on the following:

- Quantitative assessments of projected health risks at various exposure concentrations.
- Assessments of the feasibility of accurately measuring and controlling exposures to the hazard in the workplace [NIOSH, 1995a; NIOSH, 2011a; NIOSH, 2011b; NIOSH 2013].

3.0 Carcinogen Classification Systems

Authoritative bodies have developed several carcinogen classification systems, primarily to identify and classify chemicals that may raise the risk of cancer in humans. Throughout the world, regulatory agencies, governing bodies, advocacy groups, industry, consumers, and the public rely on these classification systems to assess risks of exposure to the listed chemicals. All systems have a decision logic. They include summaries of background information on specific chemicals and rationales for where the chemicals were placed in the classification system. They also all rely on scientific judgment to some extent, especially with regard to assessing the strength of evidence and quality of data. Notable systems classify carcinogens into one or several categories. The simplest systems list chemicals as either carcinogenic or unlisted. Other systems grade carcinogens based primarily on the body of evidence, but also on potency (e.g., German MAK system [DFG 2011]). Although all systems consider to some extent the consistency, quality, and reliability of the evidence, many systems give separate evidence categories (e.g., NTP, EPA, IARC) [NTP 2011; EPA 2005; IARC 2006]. Classification systems require criteria that rely on processes that involve one or more steps. One-step processes consider all acceptable data together (e.g., EPA). Multistep processes consider data sets from human, animal, or mechanistic studies separately, and then they combine the separate conclusions to reach a final conclusion (e.g., IARC, NTP). Some systems include potency, usually by defining a single dose or exposure concentration above which there is increased risk of cancer. Evaluating the classification systems leads to several observations [Cogliano 2011]: (1) Systems with more than one listing categories better reflect the state of science than systems that only identify a chemical as a carcinogen; (2) systems that document multiple steps that lead to a conclusion give greater transparency than systems that use only a single step; and (3) systems that include potency or dose-response information are more complex, but they may also increase the use of scientific evidence. The purpose of the classification systems is to inform risk management decisions and communicate risk. Several carcinogen classification systems are described below.

3.1 National Toxicology Program Report on Carcinogens

The U.S. Department of Health and Human Services (DHHS) National Toxicology Program (NTP) *Report on Carcinogens* (RoC) is a congressionally mandated listing of agents, substances, mixtures, and exposure circumstances that (1) are *known to be human carcinogens* or *may reasonably be anticipated to be human carcinogens,* and (2) represent exposure to a significant number of U.S. residents [NTP 2012]. The RoC is updated with new agents every few years and now contains 240 listings. The listing categories (*known, reasonably anticipated)* have remained unchanged since the first edition in 1980. The listing criteria and review process have evolved continuously, with several updates included in the 12th edition, released in June 2011 [NTP 2011].

For carcinogens classified as *known*, sufficient evidence from studies in humans shows that exposure to the chemical has a causal relationship to human cancer. A chemical can also be listed in this category because human studies show biological effects known to lead to cancer, but the chemical itself may not have been observed to increase the risk of cancer.

For carcinogens classified as *reasonably anticipated*, there can be (1) limited evidence of cancer in humans that makes it credible to interpret that the chemical increases the risk of cancer, but alternative explanations—such as chance, bias, or confounding factors—could not be adequately excluded; or (2) sufficient evidence of cancer in experimental animals. Alternatively, a chemical can be listed in this category if there is (3) evidence that it is a member of a class of chemicals already listed in the RoC, or if it causes biological effects known to lead to cancer.

Conclusions regarding carcinogenicity are based on scientific judgment that considers 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. The NTP does not try to rank carcinogenic hazards or do quantitative risk assessments on the likelihood of a carcinogenic response. In the 12th RoC, NTP states "the listing of substances in the RoC only indicates a potential hazard and does not establish the exposure conditions that would pose cancer risks to individuals in their daily lives."

Anyone can nominate an agent for listing in the NTP RoC. Reviewing a nomination is a multistep process that begins when the Office of the RoC prepares a background document for peer review at a public meeting. The Office of the RoC then prepares a chemical profile that recommends a listing, and an external scientific panel gives a peer review for the recommended listing and profile. The draft is then published and available for public comment before The Office of the RoC submits it to the DHHS for final review and approval.

NIOSH, the National Institute of Environmental Health Sciences, and the Food and Drug Administration comprise the three founding members of the NTP. As a founding member, NIOSH has a representative on the NTP Executive Committee, has input into prioritization of chemicals at NTP, and has a vote in all procedural matters. This close association with the NTP makes direct use by NIOSH of the NTP carcinogen classification both logical and efficient.

3.2 U.S. Environmental Protection Agency (EPA) Guidelines for Cancer Risk Assessment

(See http://www.epa.gov/cancerguidelines/.)

In 1976, the EPA issued Interim Procedures and Guidelines for Health Risk Assessments and Economic Impact of Suspected Carcinogens. The EPA guidelines have principles and procedures that EPA scientists use to assess cancer risks from chemicals or other agents in the environment

and to inform the public of those risks. EPA updated the guidelines five times, with each update going through public and scientific review. In March 2005, EPA published the most recent revision. These guidelines bring to a close a long developmental process, and they replace the EPA's original cancer risk assessment guidelines. They do not establish any rule or law, and have no binding effect on EPA or any regulated entity [EPA 1976, 1986, 2005].

In 2009, EPA revised its Integrated Risk Information System (IRIS) Assessment Development Process and gave formal steps for extensive scientific peer and public review [EPA 2009]. This plan was further revised and strengthened in July 2011 in response to National Academy of Sciences review [EPA 2011b]. IRIS uses criteria from the EPA guidelines to classify chemicals as to their carcinogenicity.

Most chemicals that EPA has considered for classifying as carcinogens were classified under either the 1986 EPA guidelines or the 2005 EPA guidelines. 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.

The 1986 guidelines gave a summary of the weight-of-evidence regarding a chemical's potential as a human carcinogen, and they placed the chemical (agent) into one of the following categories:

> *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 (i.e., indicative of a causal relationship) from animal bioassay data, but either limited human evidence (i.e., indicative of a possible causal relationship, but not exclusive of alternative explanations; *Group B1*), or with 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 noncarcinogenicity 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.

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 risk and describes conditions associated with a chemical's hazard potential. The guidelines give preference to information reported in peer-reviewed scientific journals. The narrative also gives a

summary of uncertainties and key default assumptions used. The previous six-category alphanumeric classification system was replaced with five hazard descriptors:

- 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.

"Carcinogenic to humans" requires strong evidence of human carcinogenicity that includes 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 enough weight of evidence to show carcinogenic potential in humans, but it does not reach the weight of evidence for the descriptor "carcinogenic to humans." Nevertheless, the data show 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" shows concern that the chemical may be a potential human carcinogen, but there may not be enough data for a stronger conclusion. 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" shows that 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.

When EPA publishes a chemical descriptor a narrative follows that further describes the primary basis for the weight-of-evidence, as well as any limitations to applying it based on dose-rate or dependence on key events in a mode of action. EPA recommends a critical analysis of all evidence in a single step after assessing all individual lines of evidence. Understanding the mode of action is a key step in considering the human relevance of risks. This understanding is based on animal

findings, risks to sensitive populations or life stages (for which the EPA has supplemental guidance), and by evaluating risk assessment options.

EPA's Integrated Risk Information System (IRIS) program has classified 300 chemicals [EPA 2012a]. EPA's Office of Pesticide Programs has also classified 481 chemicals into the five cancer descriptors [EPA 2012b].

3.3 IARC carcinogen classification

The IARC established its criteria system in 1971, and it was among the earliest systems to classify carcinogens. The IARC adopted its most recent criteria in 2006. The IARC review process includes procedures to select chemicals [IARC 2006]. Teams of international experts conduct IARC assessments for each chemical. Like the NTP and EPA processes, the IARC process is transparent, and the assessments are widely recognized internationally. 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 overall evaluation of evidence of carcinogenicity considers three types of evidence: animal, human, and mechanistic data. The animal or human evidence is classified by the Working Group as sufficient, limited, inadequate, or suggesting lack of carcinogenicity. 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 classification system includes these categories:

Group 1: Carcinogenic to humans
Group 2A: Probably carcinogenic to humans
Group 2B: Possibly carcinogenic to humans
Group 3: Not classifiable as to carcinogenicity to humans
Group 4: Probably not carcinogenic to humans

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.

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 generally does not convene Working Groups to evaluate agents when there is no suspicion that a chemical is a carcinogen.

3.4 Globally Harmonized System (GHS) carcinogen classification

The Globally Harmonized System of Classification and Labelling of Chemicals (GHS) was developed to harmonize classifying and labeling of chemicals internationally, including carcinogens. GHS was developed through the cooperation of the International Labour Organization (ILO), the Organization for Economic Cooperation and Development (OECD), and the United Nations Sub-Committee of Experts on the Transport of Dangerous Goods [UNECE, 2009]. The United States was part of this international agreement on classification and labeling, and the U.S. version has been codified by OSHA as part of its Hazard Communication Standard [77 Fed. Reg. 17574-17896, 2012].

The GHS carcinogen categories align to varying extents with the NTP, EPA, IARC, and other carcinogen classification systems. The OSHA Hazard Communication Standard provides a table in a non-mandatory Appendix F (Table 1) that describes an approximate alignment of GHS with NTP and IARC. The table is meant as a helpful guide to employers who may not have the resources and expertise to conduct an independent evaluation of the evidence. However, OSHA recognizes that classifiers who rely on their own weight of evidence may consider some IARC 2B agents based on sufficient evidence of carcinogenicity in experimental animals but inadequate evidence in humans to correspond to GHS category 1B instead of category 2.

Table 1. Table relating approximate equivalences among IARC, NTP RoC, and GHS carcinogenicity classifications [OSHA 2012]

Approximate Equivalences Among Carcinogen Classification Schemes		
IARC	**GHS**	**NTP RoC**
Group 1	Category 1A	Known
Group 2A	Category 1B	Reasonably Anticipated (See Note 1)
Group 2B	Category 2	

Note 1:

1. *Limited evidence of carcinogenicity from studies in humans (corresponding to IARC 2A / GHS 1B);*
2. *Sufficient evidence of carcinogenicity from studies in experimental animals (again, essentially corresponding to IARC 2A / GHS 1B);*
3. *Less than sufficient evidence of carcinogenicity in humans or laboratory animals; however:*

    a. *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" or "Reasonably Anticipated" to be a human carcinogen, or*
    b. *There is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.*

The GHS carcinogen categories and levels of evidence include [OSHA 2012]:

- Category 1 "Known or presumed human carcinogens." The classification of a substance in this category is based on the strength of evidence together with the weight of evidence considerations, as described in the OSHA Hazard Communication Standard.
    - Subcategory 1A "Known to have carcinogenic potential for humans." This category is largely based on human evidence and may be derived from human studies that establish a causal relationship between human exposure to a substance and the development of cancer.
    - Subcategory 1B "Presumed to have carcinogenic potential for humans." This classification is largely based on animal evidence and may be derived from animal experiments for which there is sufficient evidence to demonstrate animal carcinogenicity. In addition, on a case-by-case basis, scientific judgment may warrant a decision of presumed human carcinogenicity derived from studies showing limited evidence of carcinogenicity in humans together with limited evidence of carcinogenicity in experimental animals.

- Category 2 “Suspected human carcinogen” based on evidence obtained from human and/or animal studies, but which is not sufficiently convincing to place the substance in Category 1A or 1B. This classification is based on strength of evidence together with weight of evidence considerations. Such evidence may be from either limited evidence of carcinogenicity in human studies or from limited evidence of carcinogenicity in animal studies.

Under GHS, an authoritative body generally does not classify a carcinogen hazard. Instead, manufacturers have the ultimate responsibility for classifying all chemical hazards, including carcinogenicity. The European Union gave hazard classifications for 1,370 chemicals as part of the Harmonized Classification and Labeling process under the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) regulation [European Parliament and Council 2006]. This effort provided an important resource for manufacturers to use in labeling their chemicals.

4.0 NIOSH Chemical Carcinogen Classification Policy

NIOSH has updated its policy for classifying chemical carcinogens. Under this policy, NIOSH will designate a single carcinogen classification of "occupational carcinogen," replacing the previous classification, "potential occupational carcinogen." NIOSH will base its classifications on the carcinogen hazard assessments from the U.S. National Toxicology Program (NTP), the U.S. Environmental Protection Agency (EPA), and the International Agency for Research on Cancer (IARC). These agencies are highly respected for their carcinogen classification systems and their transparent and systematic reviews of the scientific evidence. NIOSH will evaluate the occupational relevance (see section 4.1) of these carcinogen designations to ensure that the appropriate hazards are accurately identified in the occupational setting. Basing the NIOSH classification on the NTP, EPA, and IARC cancer classifications will prevent effort from being duplicated, which will allow NIOSH to focus its work and resources on evaluating the carcinogenic risk to workers and developing recommendations to manage workplace risk. This will include recommended exposure limits (RELs). If NIOSH determines that the scientific basis of the carcinogen classification is occupationally relevant, the chemical will be listed by NIOSH as an occupational carcinogen, along with the specific carcinogen classification listed by the NTP, EPA, and/or IARC. NIOSH will also determine the applicable GHS carcinogen category, as described below. See Figure 1.

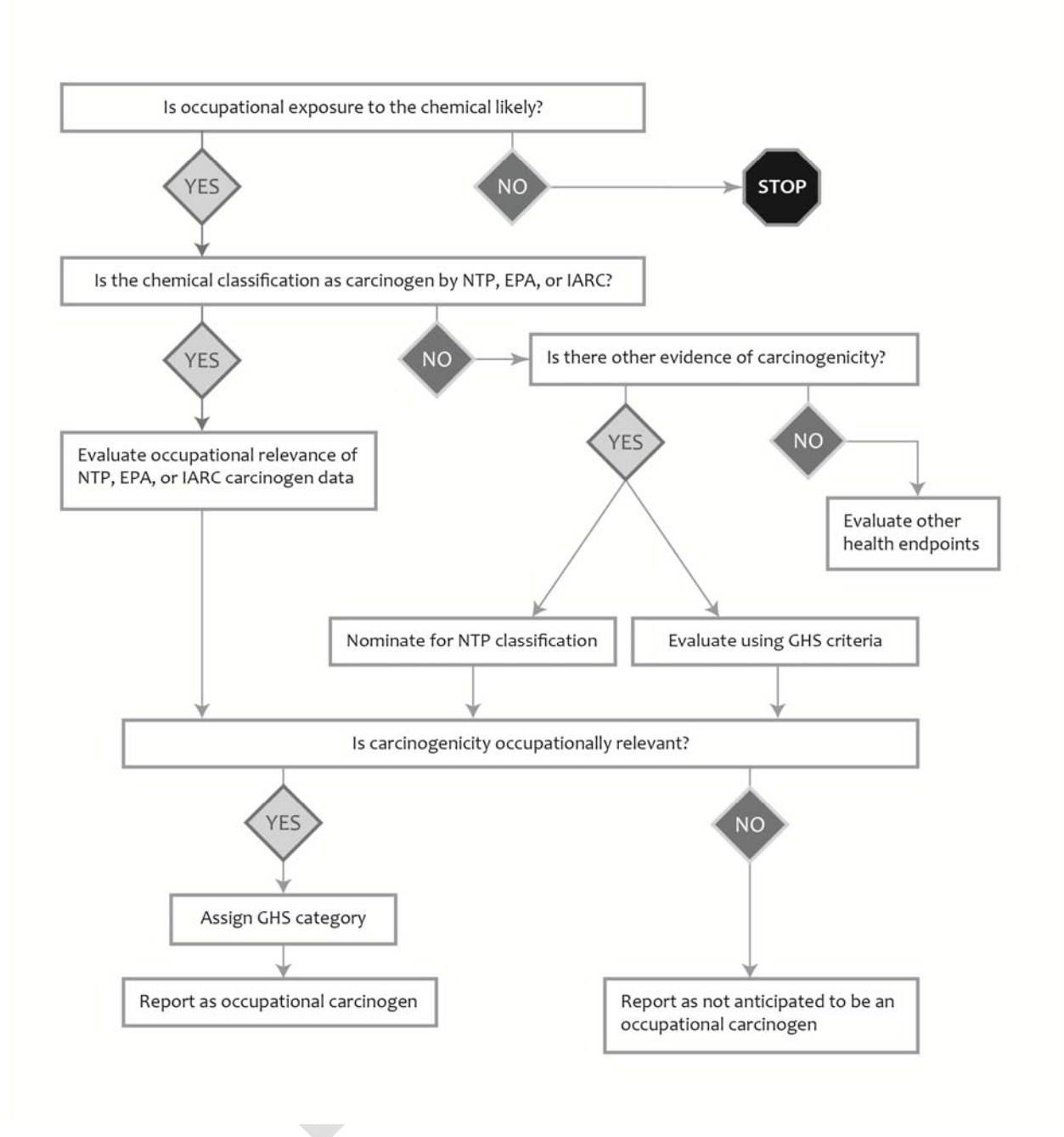

Figure 1. NIOSH chemical carcinogen review process

4.1 Occupational relevance of carcinogen classification

NIOSH will evaluate occupational relevance by first determining if workers are at risk of exposure to the chemical in the workplace. Then NIOSH will evaluate whether the scientific evidence supports a determination of "occupational carcinogen."

Chemicals with any of the following designations will be evaluated further for occupational relevance:

- 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 will evaluate the occupational relevance of these carcinogenicity classifications using the following criteria:

Potential for worker exposure

Typical workplace 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 only produced in closed systems. Workers are not likely to be routinely exposed to these intermediates in the workplace. However, the potential for release into the work environment as the result of a spill or explosion also will be considered. To demonstrate the potential for worker exposure, NIOSH will cite workplace evaluation studies and other relevant data (e.g., information on chemical use and/or job tasks known to use the chemical).

Applicability of evidence to occupational carcinogenicity

NIOSH will evaluate scientific studies to assess how the described mode of action and the route of exposure used in the studies are relevant to workplace exposures. NIOSH will first determine whether results from high-quality occupational epidemiology studies are available to assess worker cancer risks. When human evidence is not available, NIOSH

will evaluate results from animal studies to determine if they can apply to exposed workers. In general, inhalation and dermal studies conducted with animals are the most relevant because these are the typical exposures that workers encounter. However, oral or injection studies with animals may also be relevant to consider, 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. On the other hand, there may be cases where a chemical acts locally and only at an injection site. NIOSH may determine these types of studies to be less relevant to occupational cancer risk. NIOSH will evaluate animal studies as to the relevance of the reported tumor type and site, mode of action, and metabolic processes for causing cancer in humans. NIOSH would need compelling evidence to show that a chemical identified as a carcinogen by NTP, EPA, or IARC would not raise the risk of cancer to workers.

Once NIOSH has completed its review of the occupational relevance of the chemical exposure potential and the bases of the carcinogen classifications, chemicals that meet the criteria will be identified as *occupational carcinogens.*

Sometimes, agencies may determine different carcinogen classifications for the same chemical. This may be because of reasons that include different data available at the time of the assessment, or a different scientific interpretation of the same data. When these differences arise in classification, NIOSH will consider the totality of the data and the relevance of the data to the workplace. In cases where different relevant, high-quality data sets were considered by the agencies, NIOSH will adopt the classification determined to be most relevant to occupational exposures. This will be based on how recently the data were evaluated, how complete the data set was, and whether the routes of exposure, modes of action, and other considerations were relevant to workplace exposures.

A critical aspect of the NIOSH carcinogen policy is to maintain the ability to independently evaluate the quality and occupational relevance of the data. Along with considering efficiency and clarity, NIOSH seeks to classify carcinogens using a system that is appropriate and relevant to workplace exposures. Existing systems classify carcinogens encountered anywhere in the environment. To address occupational safety and health, NIOSH will evaluate both the potential for worker exposure and how the study results can apply to workers, as described above.

If a chemical NIOSH considers has not been evaluated by any of the three agencies, NIOSH will consider nominating the chemical to NTP for review. In some cases, NIOSH may decide to develop its own carcinogen classification in addition to, or in place of, nominating the chemical to the NTP. When developing a new carcinogen classification, NIOSH will use the criteria for carcinogenicity contained in the GHS [77 Fed Reg. 17574-17896 (2012)]. This entails using the

GHS criteria to classify carcinogens in order to evaluate the scientific evidence in-depth, rather than simply adopting another agency designation and assigning a GHS category.

4.2 Assigning occupational carcinogens to the GHS Carcinogen Categories

Chemicals that NIOSH determines to be *occupational carcinogens*, will be assigned Globally Harmonized System (GHS) carcinogen categories (based on guidance on the GHS as adopted by OSHA in its 2012 revision of the Hazard Communication Standard [77 Fed. Reg. 17574-17896 (2012)]). The GHS carcinogen classification will give employers useful information to more effectively communicate the chemical hazards to workers.

Interpreting the GHS criteria and aligning the cancer designations into GHS Category/Hazard phrases may vary for the same chemical across organizations and between countries. For this reason, the GHS categories NIOSH determines may not always be the same as those determined by other authoritative bodies, such as how the European Union has implemented the REACH regulation. In general, the carcinogen classifications across NTP, IARC, and EPA correspond with each other and can be grouped into similar GHS categories. (See Table 2.)

Table 2. Correspondence of carcinogen classification with GHS carcinogen categories (adapted from OSHA 2012).

NTP RoC	IARC	EPA 1986*	EPA 2005*	GHS Category/Hazard phrase
Known to be a human carcinogen	**Group 1** Carcinogenic to humans	**Group A** Human carcinogen	Carcinogenic to humans	**Category 1A** Known human carcinogen
Reasonably anticipated to be human carcinogen	**Group 2A** Probably carcinogenic to humans	**Group B1** Probable human carcinogen	Likely to be carcinogenic to humans	**Category 1B** Presumed human carcinogen
	Group 2B Possibly carcinogenic to humans	**Group B2** Probable human carcinogen		
	Group 2B Possibly carcinogenic to humans	**Group C** Possible human carcinogen	Suggestive evidence of carcinogenic potential	**Category 2** Suspected carcinogen

*NIOSH added EPA classifications based on published criteria. IARC classifications were modified from those described by the table in the OSHA Hazard Communication Standard, Appendix F. The original IARC classifications

and NTP classifications are found in the OSHA Hazard Communication Standard [77 Fed. Reg. 17574-17896 (2012]), Appendix F.

NIOSH will assign a GHS category using the criteria described in the OSHA Hazard Communication Standard [77 Fed Reg. 17574-17896 (2012)]. Those criteria, as applied to the cancer classifications of NTP, EPA, and IARC, are as follows:

NIOSH will assign the GHS Carcinogen Category 1A: *known human carcinogen* whenever any of the following conditions apply:

- NTP classifies the carcinogen as *known to be a human carcinogen*.
- EPA classifies the carcinogen as Group A: *human carcinogen* (1986 guidelines) or *carcinogenic to humans* (2005 guidelines).
- IARC classifies the carcinogen as Group 1: *carcinogenic to humans.*

In most cases, if one agency classifies a chemical in its highest level for evidence of carcinogenicity and another agency classifies it at a lower level of concern (e.g., NTP: *reasonably anticipated to be a human carcinogen* and EPA: Group A: *human carcinogen),* NIOSH will assign the GHS category that has a classification that affords the most health protection (in the example, GHS carcinogen category 1A: *known human carcinogen,* corresponding to the EPA Group A: *human carcinogen* classification). Exceptions to this might occur if NIOSH determines the data supporting carcinogenicity considered by one agency is more occupationally relevant than data considered by another agency.

The GHS carcinogen categories 1B and 2 take more consideration, because the NTP classification *reasonably anticipated to be a human carcinogen* and IARC classification 2B have criteria that overlap the two GHS categories. NIOSH will assign GHS carcinogen category 1B to chemicals classified as NTP *reasonably anticipated* or IARC 2B if there is sufficient evidence from animal studies. NIOSH will assign GHS carcinogen category 2 to chemicals classified as NTP *reasonably anticipated* or IARC 2B, which have limited evidence from animal data.

NIOSH will consider assigning the GHS Carcinogen Category 1B: *presumed human carcinogen* whenever the classifications that NIOSH reviews would not meet the criteria for GHS Category 1A, and any of the following conditions apply:

- NTP classifies the carcinogen as a *reasonably anticipated to be human carcinogen,* and sufficient evidence in animals supports the classification (according to NTP criteria).
- EPA classifies the carcinogen as Group B1: *probable human carcinogen;* or Group B2, *probable human carcinogen* (1986 guidelines); or *likely to be carcinogenic to humans* (2005 guidelines).
- IARC classifies the carcinogen as Group 2A: *probably carcinogenic to humans*.
- IARC classifies the carcinogen as Group 2B: *possibly carcinogenic to humans,* and sufficient evidence in animals supports the classification (according to IARC criteria).

NIOSH will consider assigning GHS Carcinogen Category 2: *suspected carcinogen* whenever the classifications that NIOSH reviews would not meet the criteria for GHS Category 1A or 1B, and any of the following conditions apply:

- NTP classifies the carcinogen as a *reasonably anticipated to be human carcinogen* and the evidence supporting that classification is limited in animals (according to NTP criteria).
- EPA classifies the carcinogen as Group C: *possible human carcinogen* (1986 guidelines) or as *suggestive evidence of carcinogenic potential* (2005 guidelines).
- IARC classifies the carcinogen as Group 2B: *possibly carcinogenic to humans* and the evidence supporting that classification is limited in animals (according to IARC criteria).

On a case-by-case, NIOSH will evaluate additional information on one or more of the following: (1) mode of action from human, animal and in vitro studies; (2) structural analogy to known carcinogens; and (3) limited evidence from human studies. This information may influence how NIOSH assigns the GHS Carcinogen Category, either increasing or decreasing the level of concern.

4.3 Reporting occupational carcinogens and GHS Carcinogen Categories

For chemicals NIOSH determines to be *occupational carcinogens*, NIOSH will list the NTP, EPA, and/or IARC classifications, and the assigned GHS carcinogen categories in official NIOSH publications and in *Federal Register* notices. If an agency has not evaluated a chemical, that agency would not be listed in the report.

If NIOSH determines that the NTP, EPA, or IARC carcinogen designation for a chemical will most likely not be relevant to occupational exposures, NIOSH will report why it made this determination. Reports in summary documents such as the *NIOSH Pocket Guide to Chemical Hazards* will note that *NIOSH does not consider this chemical an occupational carcinogen* and any NTP, EPA, and IARC carcinogen classifications will be reported.

4.4 Implementing the carcinogen classification policy

In this section, NIOSH uses as examples a hypothetical update to the criteria document for benzene and its associated carcinogen classifications, and a hypothetical update to the REL for heptachlor and its associated carcinogen classifications. Please note that NIOSH has not completed its classification of these chemicals, and these examples do not represent Institute policy on benzene or heptachlor. Instead, these purely hypothetical examples illustrate the steps in the process.

In considering the carcinogenicity of benzene, NIOSH would assess the classifications of NTP, EPA, and IARC. The NTP 12th RoC [NTP 2011] lists benzene as a chemical *known to be carcinogenic to humans.* The EPA IRIS documentation [EPA 2000] lists benzene as a *Group A (human carcinogen),* and the IARC monograph [IARC 2012] lists benzene as *Group 1 (carcinogenic to humans).* NIOSH would then assess occupational relevance and, assuming that NIOSH found the workplace exposures and evidence supporting carcinogen classifications to be relevant, would classify benzene as an *occupational carcinogen.* NIOSH would then assign a GHS carcinogen category, which in this case would be *Category 1A.* NIOSH might write the following in a hypothetical document:

> *In evaluating the carcinogenicity of benzene, NIOSH considered classifications from other organizations. The NTP Report on Carcinogens lists benzene as a chemical known to be carcinogenic to humans. The EPA IRIS lists benzene as Group A—human carcinogen. The IARC monograph on benzene lists benzene in Group 1—carcinogenic to humans. NIOSH concurs with these designations and confirms the occupational relevance of the carcinogen classification for benzene. NIOSH will list benzene as an occupational carcinogen based on NTP (known to be carcinogenic to humans), EPA (Group A) and IARC (Group 1) classifications. NIOSH assigns benzene a GHS carcinogen category 1A: known human carcinogen.*

Summary documentation, such as the *NIOSH Pocket Guide to Chemical Hazards,* would contain an entry with the following information:

> *Benzene*
> *NIOSH occupational carcinogen*
> *GHS carcinogen category 1A: known human carcinogen*
> *based on: NTP: known to be carcinogenic to humans*
> *EPA: Group A: human carcinogen*
> *IARC: Group 1: carcinogenic to humans*

Another way to illustrate the process is through a hypothetical NIOSH update of the REL for heptachlor. As part of identifying the hazard, the carcinogen classification protocol would be followed. Heptachlor is not listed in the NTP 12th RoC. However, EPA has evaluated heptachlor and found that heptachlor is a probable human carcinogen (Category B2) based on sufficient evidence in animals [EPA 1993]. IARC also evaluated heptachlor and found it was possibly carcinogenic to humans (Group 2B), based on sufficient data in animals [IARC 2001]. Based on this, NIOSH would provide the following information:

In evaluating the carcinogenicity of heptachlor, NIOSH considered information from EPA and IARC. The NTP 12th Report on Carcinogens did not list heptachlor. EPA IRIS documentation classifies heptachlor as a probable human carcinogen (Category B2) based on sufficient data in animals, and IARC has classified this chemical as possibly carcinogenic to humans (Group 2B), based on sufficient data in animals. NIOSH reviewed the occupational relevance of the workplace exposures and the bases for the carcinogen classifications and determines that heptachlor is an occupational carcinogen. NIOSH will list heptachlor as an occupational carcinogen based on EPA (Group B2) and IARC (Group 2B). NIOSH assigns heptachlor a GHS Category 1B: presumed human carcinogen.

Summary documentation, such as the *NIOSH Pocket Guide to Chemical Hazards*, would include an entry with the following information:

Heptachlor
NIOSH occupational carcinogen
GHS carcinogen category 1B: presumed human carcinogen
based on: EPA: Group B2-probable human carcinogen (sufficient data in animals)
IARC: Group 2B-possibly carcinogenic to humans (sufficient data in animals)

This type of summary language clarifies the source of the NIOSH classification, and the addition of the NTP, EPA, IARC, and GHS designations in summary documentation, such as the *NIOSH Pocket Guide to Chemical Hazards*, would improve communication of the hazard to workers. For risk management, the NIOSH designation of occupational carcinogen will give employers notice that they should take appropriate precautionary steps to protect workers from carcinogenic chemicals in the workplace.

Although different strategies may be recommended for hazard communication depending on the GHS category, NIOSH will provide thorough risk management guidance for all chemicals determined to be occupational carcinogens, regardless of the magnitude or sufficiency of information used to classify a carcinogen.

5.0 Target Risk Level for Carcinogen RELs

5.1 Introduction

Classifying a chemical as a carcinogen is only one step in the process to characterize risk. After classifying a chemical comes assessing the risk and establishing the REL. NIOSH will determine a candidate REL by evaluating the exposure-response relationship to find the point where risks will not exceed a given (target) level. As part of this policy, NIOSH sets a target risk level for carcinogen RELs.

As the primary federal agency that performs occupational safety and health research, NIOSH has unique expertise assessing occupational risks, which includes assessing risks from occupational carcinogens. Historically, NIOSH did not typically issue quantitative RELs for carcinogens; instead, the Institute recommended that carcinogen exposures be reduced to the lowest feasible level [NIOSH 1988b]. In 1995, NIOSH amended this policy based on a better understanding of cancer science. The 1995 policy projected exposure levels at which there may be some remaining or residual risks [NIOSH 1995b]. At that time, NIOSH did not set a target risk level for such exposures. Assuming there is no dose-response threshold for carcinogens, any exposure to a carcinogen involves some degree of excess risk. For this reason, the only way to completely eliminate the excess risk is to prevent exposure. NIOSH strongly advocates using safer alternatives to toxic chemicals, including substituting noncarcinogenic chemicals for carcinogens whenever feasible.

NIOSH conducts quantitative risk assessment by using mathematical models to describe the exposure-response relationship and to estimate low-dose risks. NIOSH derives health-based estimates of the risk of exposure at various levels during a 45-year working lifetime, and uses those estimates to set a REL. Such methods project both a central estimate of the risk associated with occupational exposure, and they also give a statistical confidence interval for that estimate. NIOSH will treat exposure-response as low-dose linear unless a nonlinear mode of action has been clearly established, in which case NIOSH will adopt a modeling approach defined by the data (including nonlinear approaches when appropriate).

Revising the NIOSH carcinogen and REL policy has raised the issue of how to set a target risk level for carcinogen RELs. Specifically, for occupational settings, should NIOSH set a 1 in 1,000 working lifetime excess risk as the target level for an REL, or should the Institute consider a lower target risk level? The 1 in 1,000 risk level comes from interpreting the 1980 U.S. Supreme Court "benzene" decision, which determined a 1 in 1,000 excess risk to be significant. The history of this target level is explained more fully in section 5.2. The question of target risk level arises because of a characteristic feature of using a risk assessment model for carcinogens. In general, whether the model forms are linear or nonlinear, any non-zero exposure to a carcinogen is expected to

yield some excess risk of cancer. The excess risk estimate for low exposures may be very small, but unless a dose-response threshold exists, the excess risk will be greater than zero. Historically, NIOSH has assumed that the dose-response relationship for carcinogens does not have a threshold [Fairchild 1976]; that is, it is assumed that there is no nonzero dose below which the excess risk is zero. If NIOSH bases RELs for carcinogenic chemicals on the results of quantitative risk assessment modeling, a policy must be in place that sets the target risk level of the proposed REL.

The mode of action for carcinogens can affect the mathematical modeling assumptions and change the way quantitative risk assessment is conducted. Genotoxic (DNA-damaging) carcinogens are presumed to act via nonthreshold mechanisms, and occupational exposure limits (OELs) for these chemicals are typically based on low-dose linear models. It is often assumed that carcinogens—which act through nongenotoxic mechanisms, such as hormonal imbalance or 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 nonthreshold, 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 sublinear but nonthreshold models to the experimental data [NIOSH 2011a]. 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, nonlinear modeling approaches for nongenotoxic or indirectly genotoxic carcinogens do require setting a target risk level to develop an OEL.

5.2 History of the NIOSH target risk level for carcinogens

The process to develop a target risk level for occupational carcinogens has a long history. The Occupational Safety and Health (OSH) Act of 1970 [29 USC 651] guides the developing of NIOSH's REL, but it does not provide a numerical value for the target risk level. The OSH Act directs NIOSH 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, the exposure levels at which no employee will suffer impaired health or functional capacities or diminished life expectancy as a result of his work experience." The law does not further define the term "safe."

Barnard [1990] noted that "safe" and "significant risk" are interrelated in terms of their concept and origin. The legal definitions of these terms were discussed in two major court cases—the U.S. Supreme Court "benzene" decision [Industrial Union Dept. 1980] and the U.S. Court of Appeals for the District of Columbia Circuit "vinyl chloride" decision [Natural Resources Defense Council

1987]. In the benzene decision, the U.S. Supreme Court noted that "safe" does not mean "risk free," because many normal activities involve some risk and are generally considered safe. Instead, the court ruled the regulatory agency had the burden to show that long-term exposure to benzene at a given level presents "a significant risk of material health impairment."

In the 1980 U.S. Supreme Court "benzene" decision, the court wrote, "It is the Agency's responsibility to determine, in the first instance, what it considers to be a 'significant' risk. Some risks are plainly acceptable and others are plainly unacceptable. If, for example, the odds are one in a billion that a person will die from cancer by taking a drink of chlorinated water, the risk clearly could not be considered significant. On the other hand, if the odds are one in a thousand that regular inhalation of gasoline vapors that are 2% benzene will be fatal, a reasonable person might well consider the risk significant and take appropriate steps to decrease or eliminate it." Therefore, although the Court did not explicitly set a level of "significant" risk, it did imply that a 1 in 1,000 lifetime excess risk is significant, while a 1 in 1 billion risk is not, indicating that the threshold for a "significant" risk must lie within this interval.

Rodricks et al. [1987] evaluated the risks of work-related deaths in various industries and, based on data from 1984, concluded that "a 1 in a 1,000 risk level is low compared to other fatality hazards in jobs commonly thought of as 'safe.'" They noted that both the wholesale and retail trade sector and the services sector had lifetime fatality rates between 1 and 2 per 1,000 employees. Travis and Hattemer-Frey [1988] reviewed federal regulatory decisions for carcinogenic risks and found that "every chemical with an individual lifetime cancer risk above about 1 in 1,000 historically has been regulated." For chemical exposures to large populations, the risk level of concern is 1 in 10,000. Their review concludes that both the lifetime individual risk and the estimated total cancer incidence (i.e., the number of excess cancer cases) must be considered in evaluating whether a chemical exposure poses an acceptable risk of cancer. They note that "past regulatory decisions indicate that in many circumstances risks greater than 1 in 10,000 are in fact tolerated," and consider a population-based risk level of 1 in 10,000, ranging to 1 in 1,000, to indicate a *de manifestis* risk level (i.e., "a ceiling above which events are inherently unsafe and should be regulated without regard for cost").

5.3 NIOSH precedent for using 1 in 1,000 as a target risk level

NIOSH policy for setting carcinogen RELs has varied over the years, from setting RELs "as low as feasible" without numerical RELs, to setting RELs that correspond to a target risk level of 1 in 1,000 working lifetime excess risk. NIOSH used the 1 in 1,000 target risk level to set several RELs for chemicals with serious adverse health effects, including carcinogens. In 1986, NIOSH used a cancer risk assessment for benzene to derive a health-based REL corresponding to a 1 in a 1,000 risk of cancer for a working lifetime [NIOSH 1986]. The 1995 criteria document for coal mine dust discussed 1 in a 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 a 1,000 as the risk level for carcinogenic effects in setting RELs [NIOSH 1986, 1995a, 2011a, 2013].

5.4 New NIOSH policy for a target risk level for setting RELs

To conform with Section 20(a)(3) of the OSH Act, NIOSH recommends that exposure to carcinogens be kept below a target risk level of 1 in 1,000 excess cancer cases in a working lifetime. NIOSH interprets the guidance of the U.S. Supreme Court in the "benzene" decision [Industrial Union Dept. 1980] as establishing that a 1 in a 1,000 lifetime excess risk is significant. Although this legal decision does not pertain specifically to NIOSH, the Institute will continue to use the "benzene" decision as guidance for establishing RELs for occupational carcinogens. Therefore, NIOSH will recommend that exposures be kept below a target risk level of 1 in 1,000 cancer cases in a working lifetime. This will be applied except in unusual circumstances that would lead to selecting another REL. These unusual circumstances could involve concerns about the analytical measurement feasibility or other issues. In applying this policy, NIOSH will set RELs (1) for chemical carcinogens at the target risk level expected to produce a cancer risk of 1 in 1,000 during a 45-year working lifetime exposure, and (2) when the REL can be measured in a way that is judged to be analytically achievable, as described in section 6. Keeping exposures within the target risk level of 1 in 1,000 is the *minimum* level of protection, however. Controlling exposure to lower concentrations is always warranted, because an excess risk of 1 in 1,000 is one or more orders of magnitude higher than what the United States permits for the general public.

When using epidemiologic data to set the REL, NIOSH has historically based the REL on the maximum likelihood estimate, or central estimate, of the dose producing a 1 in 1,000 lifetime excess risk [NIOSH, 2011b, 2013]. In contrast, when the REL has been based on experimental animal data, NIOSH has historically based the REL on the 95% lower confidence limit estimate of the dose producing a 1 in 1,000 lifetime excess risk [NIOSH, 2011a]. Under the new policy, NIOSH will project both a central estimate and a 95% lower confidence limit, and the REL will typically be based on the 95% lower confidence limit.

NIOSH will evaluate carcinogens using risk-based exposure limits, and the NIOSH recommendation will be based on a quantitative risk assessment (QRA) conducted on the best available data. Based on this QRA, NIOSH will communicate an array of risk levels, from 1 excess cancer case in 100 workers, to 1 excess cancer case in 1 million workers. For carcinogens where the 1 in 1,000 risk level is below the limit of quantitation (LOQ) of the current NIOSH analytical method [NIOSH 1994] (or other validated analytical equivalent), the LOQ will be the default REL. This REL can be revised to a lower LOQ when more accurate analytical methods are developed.

6.0 Analytical Feasibility and Engineering Achievability

6.1 Introduction

To protect health, RELs are set primarily using a quantitative risk assessment, when the data permit. However, the feasibility of measuring a chemical at the REL concentration and the ability to limit exposures using engineering controls also play important roles. NIOSH recommendations on the technical feasibility of an analytical method and achievability of engineering controls have evolved over time.

6.2 History

In 1988, NIOSH used the phrases "lowest feasible limit," "lowest feasible level," and "fullest extent feasible" interchangeably in NIOSH testimony to OSHA for rulemaking on air contaminants. 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 1988b, p. 20]. NIOSH also stated in its 1988 testimony on air contaminants that if NIOSH considered a chemical a "potential occupational carcinogen," then such exposures should be reduced to the "fullest extent feasible" or "lowest feasible limit," or "lowest feasible level." Under the 1988 policy for potential occupational carcinogens, RELs for most carcinogens were non-quantitative values labeled "lowest feasible concentration."

As stated in section 2, the current NIOSH [1995b] REL policy states the following:

> "NIOSH RELs will be based upon risk evaluations using human or animal health effect 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." (Emphasis added.)

NIOSH [1995b] stated "… this comprehensive description of risks and the reality of the workplace will better serve all our customers, OSHA and MSHA, employers, and workers, by improving the quality of debate on working conditions." RELs developed under this policy are syntheses of quantitative risk assessment (when data permit), analytical measurement limits, and analysis of the achievability of the REL in the workplace.

In 2006, NIOSH published the criteria document on refractory ceramic fibers that included the terminology "feasible" and "achievable" when controlling exposures to the REL [NIOSH 2006]. The terminology of "achievability" and achievable has been used to describe engineering controls in the criteria document for hexavalent chromium [NIOSH 2013] and the draft criteria document for diacetyl/2,3-pentanedione [NIOSH 2011b].

6.3 Relevant factors in current Policy

Users of the NIOSH RELs do not always recognize that sometimes the feasibility of analytical methods [NIOSH 1994] and achievability of engineering controls are included in an REL. Often, REL users wrongly assume that all RELs are based solely on preventing health effects. In fact, some RELs are based on analytical limitations, or the inability to routinely control exposures with engineering controls. For example, the existing policy has resulted in some RELs being based on the limit of quantitation, limit of detection, or reliable quantitation limit of the sampling and analytical method. These sometimes are at a higher exposure concentration than those derived for the health-based REL.

6.4 NIOSH policy for assessing analytical method "feasibility" and engineering control "achievability" in the development of RELs

NIOSH is revising its method to develop RELs by changing the way it considers analytical feasibility and engineering achievability (Figure 2). First, NIOSH derives the health-based risk estimate as described in section 5. Then NIOSH evaluates whether airborne exposures to the chemical can be accurately measured and controlled in the workplace. This is described below.

6.4.1 Analytical feasibility

Given the importance of evaluating worker exposures, a sampling and analytical method must be available to accurately measure exposures at the REL. NIOSH will evaluate all existing analytical methods for the chemical and determine whether a method exists that is partially or fully validated. If a method does not exist, NIOSH will recommend research to develop a reliable method. In cases where an analytical method already exists, but the limit of quantitation is higher than the health-based target risk level, NIOSH will set the REL at the limit of quantitation of the sampling and analytical method. Research will be considered to improve the sensitivity and accuracy of the method. When NIOSH sets the REL at the limit of quantitation, or reliable quantitation limit, NIOSH will publish the REL with an "AF" notation (for analytical feasibility). This notation alerts users that the REL is not set at the health-based target risk level, but instead it reflects the limitations of the sampling and analytical method.

6.4.2 Engineering achievability

A long-used framework to control exposures in the occupational environment consists of substitution, isolation, and ventilation, followed by administrative programs [NIOSH 1973]. This hierarchy of controls mitigates risks for workers by stepping through various options for control. Elimination and substitution are the first two tenets of the hierarchy, followed by using engineering controls. The hierarchy of controls is widely used as an effective strategy for controlling workplace hazards [Ellenbecker 1996; Halperin 1996; Weinberg et al. 2009].

NIOSH recommends using the hierarchy of controls to reduce exposures in the workplace. NIOSH, however, will no longer specifically consider engineering achievability for each chemical-specific REL. NIOSH will evaluate the capability for controlling airborne exposures with engineering controls in concert with the supporting documentation that accompanies a NIOSH REL policy document. If NIOSH lacks adequate exposure measurement/control data, the absence of such data will be explained when the REL is set and NIOSH will recommend that research be conducted to determine the efficacy of existing engineering controls. NIOSH will give recommendations that reflect the availability and efficacy of existing controls, including alternative risk management practices to reduce worker exposures.

6.4.3 Notations

Figure 2 gives an overview of how NIOSH uses the feasibility of the analytical method in deriving the REL. The new notation "AF" in official NIOSH publications, such as the *NIOSH Pocket Guide to Chemical Hazards,* will highlight the NIOSH practice of considering analytical feasibility in REL development. NIOSH intends for this notation to lessen the misperception that all RELs are based solely on quantitative risk assessment of the health effects of chemical exposure.

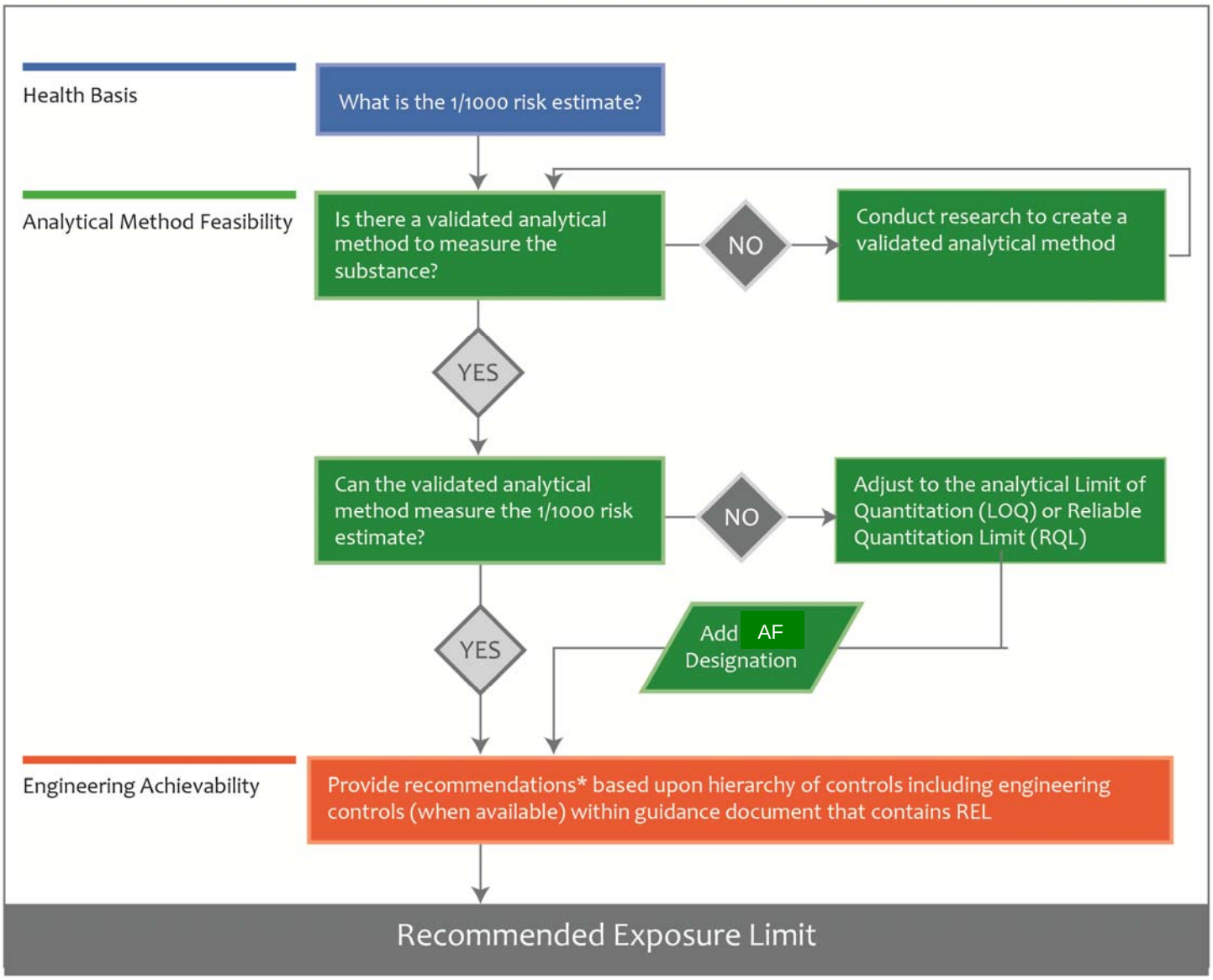

Figure 2. NIOSH policy for assessing analytical method "feasibility" and engineering control "achievability" in developing RELs.

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