# Procedures for Developing the NIOSH List of Hazardous Drugs in Healthcare Settings

**Centers for Disease Control and Prevention**
National Institute for Occupational Safety and Health

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

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# Foreword

In 2004, the National Institute for Occupational Safety and Health (NIOSH) published *Preventing Exposures to Antineoplastic and Other Hazardous Drugs in Healthcare Settings*. This NIOSH *Alert* included a sample list of drugs that can be hazardous to healthcare workers with potential occupational exposure to those who handle, prepare, dispense, administer, or dispose of these drugs. The purpose of the *Alert* was to increase awareness among workers in healthcare settings and their employers about the health risks posed by working with hazardous drugs and to provide them with measures for protecting their health. NIOSH has periodically updated that list from 2010 through 2016 as the *NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings (List)*.

This document, *Procedures for Developing the NIOSH List of Hazardous Drugs in Healthcare Settings,* provides information about how the NIOSH *List* is developed and updated and how reevaluations can be requested. This information may be useful for healthcare facilities to examine new drugs and establish their own hazardous drug list. Find the latest information, including current publications, at **NIOSH Hazardous Drug Exposures in Healthcare**.

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# List of Acronyms

| | |
|---|---|
| CBER | Center for Biologics Evaluation and Research |
| CDER | Center for Drug Evaluation and Research |
| CERHR | Center for the Evaluation of Risks to Human Reproduction |
| CFR | Code of Federal Regulations |
| DHHS | Department of Health and Human Services |
| EPA | Environmental Protection Agency |
| FDA | Food and Drug Administration |
| FOIA | Freedom of Information Act |
| IARC | International Agency for Research on Cancer |
| ME | molecular entity |
| MRHD | maximum recommended human dose |
| MSHI | manufacturer's special handling information |
| NIOSH | National Institute for Occupational Safety and Health |
| NTP | National Toxicology Program |
| OEL | occupational exposure limit |
| OHAT | Office of Health Assessment and Translation |
| USC | United States Congress |

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# Contents

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# Procedures for Developing the NIOSH List of Hazardous Drugs in Healthcare Settings

## I. Authority

The Occupational Safety and Health Act of 1970.[1]

## II. Purposes

### A. Methodology for Adding Drugs to the *List*

This *Procedures for Developing the NIOSH List of Hazardous Drugs in Healthcare Settings (Procedures)* document describes the methodology the National Institute for Occupational Safety and Health (NIOSH) uses to determine whether a drug[2] meets the criteria in the NIOSH definition of a hazardous drug.[3] Drugs that meet the NIOSH definition of a hazardous drug are placed on the ***NIOSH List of Hazardous Drugs in Healthcare Settings***.

### B. Requests to Add, Remove, or Move a Drug Between Tables of the *List*

The *Procedures* also sets forth procedures for a party to request that NIOSH (1) add a new drug to the *List*, (2) reevaluate its decision to place, or not to place, a drug on the *List* and thereby remove the drug from the *List*, or (3) reevaluate its decision to place a drug on a particular table[4] of the *List* and thereby move the drug to another table of the *List*.

### C. Use of the *List* in Healthcare and Other Settings

The *List* is designed to assist employers in identifying which drugs routinely handled by employees are considered by NIOSH to be hazardous drugs. NIOSH recommends using the *List* in conjunction with NIOSH risk management recommendations provided in *Managing Hazardous Drug Exposures: Information for Healthcare Settings (Managing Exposures)*. The recommendations are designed to assist employers in establishing hazardous drug management procedures specific to their workplace. The document is available through the **NIOSH Hazardous Drug Exposures in Healthcare** website.

In addition to healthcare facilities, the *List* may also be applied in veterinary care settings, drug research laboratories, retail pharmacies, and home healthcare agencies. Occupational groups in these settings include pharmacy personnel, nursing personnel, physicians,

[1] 29 USC § 651 *et seq*.

[2] For the purpose of the *Procedures* and the *List*, NIOSH adopts the U.S. Food and Drug Administration (FDA) definition of "drug" to include a substance recognized by an official pharmacopoeia or formulary; a substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of a disease; a substance (other than food) intended to affect the structure of any function of the body; a substance intended for use as a component of a medicine but not a device or a part or accessory of a device. Although biological products ("biologics") are included in the FDA definition, they are not included in the drugs that NIOSH evaluates for potential inclusion on the *List*. *See* Section IV and Drugs@FDA Glossary of Terms at **https://www.fda.gov/drugs/informationondrugs/ucm079436.htm#D**.

[3] For the NIOSH definition of a hazardous drug, see Section IV.

[4] The *List* contains two tables. *See* Section V.C.7 (Step 3) for a description of the tables.

physician assistants, operating room personnel, environmental services workers, research laboratorians, veterinary care workers, shipping and receiving personnel, and other potentially exposed personnel.[5, 6] The *List*, and all subsequent updates, are advisory in nature and informational in content.

# III. Background

## A. Exposure to Drugs in Healthcare Settings

Workers in healthcare and related settings may be exposed to drugs while performing job tasks such as receipt, storage, preparation, compounding or similar manipulation, dispensing, transporting, administration, other patient care activities, and during spill cleanup, and/or disposal of drugs and patient waste. For the purposes of the *Procedures,* these activities are collectively referred to as "handling." Potential routes of exposure to hazardous drugs for workers in healthcare settings include inhalation (breathing), ingestion (consuming), dermal (skin) and mucosal membrane (eyes) absorption, and percutaneous (needle puncture).[6]

## B. Health Effects From Exposure to Drugs in Healthcare Settings

Although the exposures workers in healthcare settings may receive are typically lower than the therapeutic doses administered to patients undergoing medical treatment, "[any] clinically significant pharmacologic effect occurring as a result of occupational exposure is considered undesirable, even if it can be argued that the effect is therapeutically beneficial."[7]

Exposure to various types of drugs used in patient care may increase the probability of an adverse health effect in a healthcare worker including (1) acute health effects, such as skin rashes, and mucous membrane irritation;[8] (2) chronic health effects, including cancer;[9] and (3) adverse reproductive events, such as infertility, spontaneous abortions, and congenital malformations.[10]

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[5]The *Alert* and *List* are not intended for use by workers or employers during pharmaceutical manufacturing because those worksites are not considered by NIOSH to be healthcare settings.

[6]NIOSH [2004]. NIOSH Alert: preventing occupational exposures to antineoplastic and other hazardous drugs in health care settings. By Burroughs GE, Connor TH, McDiarmid MA, Mead KR, Power LA, Reed LD, Coyle BJ, Hammond DR, Leone MM, Polovich M, Sharpnack DD. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2004-165, available at **https://www.cdc.gov/niosh/docs/2004-165/**.

[7]Naumann BD, Sargent EV [1997]. Setting occupational exposure limits for pharmaceuticals. Occup Med *12*(1):67–80.

[8]Eisenberg S [2009]. Safe handling and administration of antineoplastic chemotherapy. J Infus Nurs *32*(1):23–32; Massoomi F, Neff B, Pick A, Danekas P [2008]. Implementation of a safety program for handling hazardous drugs in a community hospital. Am J Health Syst Pharm *65*:861–865; Krstev S, Perunicic B, Vidakovic A [2003]. Work practice and some adverse health effects in nurses handling antineoplastic drugs. Med Lav *94*:432–439.

[9]Connor TH, McDiarmid MA [2006]. Preventing occupational exposures to antineoplastic drugs in health care settings. CA Cancer J Clin *56*:354–365; Lie JA, Kjaerheim K [2003]. Cancer risk among female nurses: a literature review. Eur J Cancer Prev *12*:517–526; Ratner PA, Spinelli JJ, Beking K, Lorenzi M, Chow Y, Teschke K, Le ND, Gallagher RP, Dimich-Ward H [2010]. Cancer incidence and adverse pregnancy outcome in registered nurses potentially exposed to antineoplastic drugs. BMC Nurs *9*:15; Suspiro A, Prista J [2011]. Biomarkers of occupational exposure do [*sic*] anticancer agents: a mini-review. Toxicol Lett *207*:42–52.

[10] Connor TH, Lawson CC, Polovich M, McDiarmid MA [2014]. Reproductive health risks associated with occupational exposures to antineoplastic drugs in health care settings: a review of the evidence. J Occup Environ Med *56*:901–910; Lawson CC, Rocheleau CM, Whelan EA, Lividoti Hibert EN, Grajewski B, Spiegelman D, Rich-Edwards JW [2012]. Occupational exposures among nurses and risk of spontaneous abortion. Am J Obstet Gynecol *206*:327.e1-8; NTP [2019]. NTP monograph on the systematic review of occupational exposure to cancer chemotherapy agents and adverse health outcomes. Monograph 5. Research Triangle Park, NC: National Toxicology Program; Selevan SG, Lindbohm ML, Hornung RW, Hemminki K [1985]. A study of occupational exposure to antineoplastic drugs and fetal loss in nurses. N Engl J Med *313*(19):1173–1178.

## IV. NIOSH Definition of a Hazardous Drug

The NIOSH definition of a "hazardous" drug is a drug that is

**A. Approved for use in humans[11] by the Food and Drug Administration's (FDA) Center for Drug Evaluation and Research (CDER),[12]**

**B. Not otherwise regulated by the U.S. Nuclear Regulatory Commission,[13] and**

**C. Either**

1. Is accompanied by prescribing information in the "package insert"[14] that includes a manufacturer's special handling information (MSHI),[15] or

2. Is determined to be a carcinogenic hazard, developmental hazard, reproductive hazard, genotoxic hazard, or other health hazard by exhibiting one or more of the following toxicity criteria in humans, animal models, or in vitro systems:

   - Carcinogenicity,
   - Developmental toxicity (including teratogenicity),
   - Reproductive toxicity,
   - Genotoxicity,
   - Organ toxicity at low doses,[16] or a
   - Structure and toxicity profile that mimics existing drugs determined hazardous by exhibiting any one of the previous five toxicity types.[6]

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[11]Although only drugs approved by FDA for use in humans are included in the definition of hazardous drug, some of those drugs may be used in veterinary settings for treatment of animals and may be a hazard for veterinary care workers.

[12]Although biological products, such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, recombinant therapeutic proteins, are included in FDA definition of a drug, they are not included in the drugs that NIOSH evaluates for potential inclusion on the *List* because they are approved for use by FDA's Center for Biologics Evaluation and Research (CBER), not by FDA's CDER. This provision makes clear NIOSH's long-standing practice of only considering drugs approved by FDA CDER.

[13]10 CFR Parts 19, 20, and 35. *See* **https://www.nrc.gov/materials/miau/med-use.html**. Drugs regulated by the Nuclear Regulatory Commission are not included on the *List*.

[14]*See* Drug Advertising: A Glossary of Terms at **https://www.fda.gov/drugs/resourcesforyou/consumers/prescriptiondrugadvertising/ucm072025.htm**. "Prescribing information is also called product information, product labeling, or the package insert ("the PI"). It is generally drafted by the drug company and approved by FDA. This information travels with a drug as it moves from the company to the pharmacist. It includes the details and directions healthcare providers need to prescribe the drug properly. It is also the basis for how the drug company can advertise its drug. The prescribing information includes such details about the drug as: its chemical description; how it works; how it interacts with other drugs, supplements, foods, and beverages; what condition(s) or disease(s) it treats; who should not use the drug; serious side effects, even if they occur rarely; commonly occurring side effects, even if they are not serious; effects on specific groups of patients, such as children, pregnant women, or older adults and how to use it in these populations."

[15]MSHI includes language that informs those handling the drug of the need to follow heightened handling and disposal procedures. For example, language such as "follow special handling and disposal procedures" or "procedures for proper handling and disposal of anticancer drugs should be considered" is frequently used in package inserts. However, NIOSH does not consider language pertaining to packaging and temperature controls as MSHI.

[16]All drugs have toxic side effects, but some exhibit toxicity at low doses. The level of toxicity reflects a continuum from relatively nontoxic to production of toxic effects in patients at low doses (for example, a few milligrams or less). For example, a daily therapeutic dose of 10 milligrams per day (mg/day) or a dose of 1 milligram per kilogram (mg/kg) per day in laboratory animals that produces serious organ toxicity, developmental toxicity, or reproductive toxicity has been used by the pharmaceutical industry to develop occupational exposure limits (OELs) of less than 10 micrograms per cubic meter ($\mu g/m^3$) after applying appropriate uncertainty factors. See Naumann BD, Sargent EV [1997]. Setting occupational exposure limits for pharmaceuticals. Occup Med *12*(1):67–80; Sargent EV, Kirk GD [1988]. Establishing airborne exposure control limits in the pharmaceutical industry airborne exposure control limits in the pharmaceutical industry. Am Ind Hyg Assoc J *49*(6):309–313; Sargent EV, Naumann BD, Dolan DG, Faria EC, Schulman L [2002]. The importance of human data in the establishment of occupational exposure limits. Hum Ecol Risk Assess *8*(4):805–822. OELs in this range are typically established for potent or toxic drugs in the pharmaceutical industry.

However, if a drug also exhibits a molecular property[17] that may limit the potential for adverse health effects from exposure to the drug in healthcare workers, it may be determined it is not a hazard.

## V. Identifying, Screening, Evaluating, and Reviewing a Drug for Placement on the *List*[18]

NIOSH uses a sequential approach to determine whether a drug approved by FDA CDER meets the criteria in the NIOSH definition of a hazardous drug.

### A. Step 1: Identifying Potentially Hazardous Drugs

1. NIOSH reviews the following FDA databases to identify drugs to be screened and evaluated for placement on the *List*:
   a. *Drugs@FDA: FDA Approved Drug Products* by month.[19] This FDA database lists new molecular entities (NME)[20] with new drug applications[21] and biologics license applications.[22]
   b. *Drug Safety-related Labeling Changes*.[23] This FDA database identifies drugs with new safety labeling changes (new boxed warnings[24] and/or warnings and precautions) or new pregnancy and lactation labeling information.[25]
2. NIOSH may also consider a request to add a drug to the *List*. Requests to add a drug must be submitted in writing to the NIOSH Director, include toxicity information from the package insert or any of the sources in Section V.C (Step 3) and explain how the drug meets the NIOSH definition of hazardous drug.[26]
   a. If the request for an evaluation does not provide information that suggests a toxic effect that may meet one or more of the criteria in the NIOSH definition of a hazardous drug, then NIOSH will deny the request and notify the requester in writing explaining the decision. The drug is placed in Category 1. See Section V.E (Step 5).
   b. If the provided toxicity information suggests a toxic effect that may meet one or more of the criteria in the NIOSH definition of a hazardous drug, then NIOSH

[17]Properties of a drug molecule that may limit adverse effects in healthcare workers are typically chemical, physical, and structural properties that affect its absorption (ability to enter the cells of the body), e.g., chemical structure, molecular weight, or mass. *See* Clementi F, Fumagalli G [2015]. Molecular pharmacology. Hoboken, NJ: Wiley & Sons; Di L, Kerns EH [2016]. Drug-like properties: concepts, structure, design, and methods. Oxford, UK: Elsevier; Mattson P, Kihlberg J [2017]. How big is too big for cell permeability? J Med Chem *60*(5):1662–1664, **https://doi.org/10.1021/acs.jmedchem.7b00237**.

[18]See Figure 1 for a diagram of the NIOSH procedures for identifying, screening, evaluating, and reviewing a drug for placement on the *List*.

[19]See **https://www.accessdata.fda.gov/scripts/cder/daf/**.

[20]See Drugs@FDA Glossary of Terms at **https://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm#N**. ("An NME is an active ingredient that contains no active moiety that has been previously approved by the Agency in an application submitted under Section 505 of the Federal Food, Drug, and Cosmetic Act, or has been previously marketed as a drug in the United States.")

[21]21 CFR Part 314.

[22]21 CFR Part 601.

[23]See **https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/**.

[24]See Drug Advertising: A Glossary of Terms at **https://www.fda.gov/drugs/resourcesforyou/consumers/prescriptiondrugadvertising/ucm072025.htm**. "Drugs that have special problems, particularly ones that may lead to death or serious injury, may have this warning information displayed within a box in the prescribing information. This is often referred to as a 'boxed' or 'black box' warning."

[25]21 CFR § 201.57(c)(9)(i) and (ii) and 21 CFR § 201.80. Although rare, NIOSH notes any labeling changes that could affect the status of a drug that NIOSH has previously placed on the *List*.

[26]Requests can be sent to the following address: NIOSH, 395 E Street, S.W., Suite 9200, Washington, D.C. 20201.

will evaluate the drug during the next evaluation cycle to determine if it will be proposed, or not be proposed, for addition to the *List*. Go to Section V.C (Step 3).

**B. Step 2: Screening Potentially Hazardous Drugs**

1. NIOSH screens the identified drugs to determine whether

   a. The drug package insert specifies MSHI or

   b. Information in the drug package insert[27] suggests that a drug may exhibit at least one of the types of toxicity criteria found in the NIOSH definition of a hazardous drug.

2. Screening Outcomes

   a. Manufacturer's Special Handling Information (MSHI)

   If the drug package insert contains MSHI, NIOSH will place the drug on the *List*. NIOSH will post notice of the addition on the most recent *List* website, accessible through the **NIOSH Hazardous Drug Exposures in Healthcare** website.[28] Go to Section V.F (Step 6) for placement on the *List*.

   b. Insufficient Toxicity Information in the Drug Package Insert to Meet the NIOSH Definition of Hazardous Drug[29]

   If there is insufficient information in the drug package insert to suggest that the drug exhibits any one of the toxicity criteria in the NIOSH definition of hazardous drug, then NIOSH will not propose to add the drug to the *List*. Go to Section V.E (Step 5) for categorical determination.

   c. Information in the Drug Package Insert Shows No Toxic Effect, or Shows a Toxic Effect that Does Not Meet the NIOSH Definition of a Hazardous Drug

   If information in the drug package insert shows no toxic effect or shows a toxic effect that does not meet the hazard identification criteria in the NIOSH definition of hazardous drug, then NIOSH will not propose to add the drug to the *List*. Go to Section V.E (Step 5) for categorical determination.

   d. Available Information in the Drug Package Insert Suggests a Toxic Effect

   If available toxicity information in the drug package insert suggests a toxic effect that may meet one or more of the criteria in the NIOSH definition of a hazardous drug, then NIOSH will evaluate the drug to determine if it will be proposed, or not be proposed, for addition to the *List*. Go to Section V.C (Step 3) for further evaluation.

**C. Step 3: Evaluating Potentially Hazardous Drugs**

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[27] Although the *entire* drug package insert is examined, certain specific sections may indicate that the drug exhibits at least one of the types of hazard information (toxicity) criteria found in the NIOSH definition of hazardous drug: package inserts for drugs approved prior to FDA's drug labeling regulations may not include those specific numbered sections although the same type of content is included. *See* 21 CFR §§ 201.56(b)(1) and 201.80. Section 1: Box warning, if available [21 CFR § 201.57(c)(1)]; Section 5: Warnings and Precautions (any organ toxicity, carcinogenicity, or embryo-fetal toxicity) [21 CFR § 201.57(c)(6)]; Section 6: Adverse Reactions (any post-marketing experience reported by the manufacturer)[21 CFR § 201.57(c)(7); Section 8: Use in Special Populations (pregnancy information, any human animal development toxicity) [21 CFR § 201.57(c)(9)]; Section 13: Non-clinical toxicology (animal data on carcinogenesis, mutagenesis and impairment of fertility)[21 CFR § 201.57(c)(14)]; Section 15: References, if available [21 CFR § 201.57(c)(16)]; and Section 16: Storage and Handling, if available (special handling or disposal information for workers) [21 CFR § 201.57(c)(17)].

[28] *See* **https://www.cdc.gov/niosh/topics/hazdrug/default.html**.

[29] "Insufficient" in this context indicates that in some cases, in its review of all available information, FDA did not find a concern for toxicity of a particular type and such tests were not required or that the available toxicity data are insufficient to meet the NIOSH criteria for a hazardous drug.

1. Sources of Toxicity Information for Evaluating Screened Drugs When Available Information Suggests Toxic Effect (Section V.B.2.d, Step 2).

   NIOSH may consult the following sources of information to evaluate each screened drug for potential toxic effect:

   a. Information in the drug package insert.

   b. FDA information pertaining to new drug safety labeling changes.[30]

   c. Molecular properties of the drug from available sources, such as safety data sheets (SDSs).

   d. When available, relevant information about carcinogenicity from

      i. the National Toxicology Program (NTP) within the U.S. Department of Health and Human Services,[31] and

      ii. the World Health Organization's International Agency for Research on Cancer (IARC).[32]

   e. When available, relevant information about reproductive toxicity, teratogenicity, or developmental toxicity from the NTP Center for the Evaluation of Risks to Human Reproduction (CERHR),[33] and from its successor, the Office of Health Assessment and Translation (OHAT),[34]

   f. When available, published, peer-reviewed scientific literature about the hazard potential of a particular drug, including any animal or human studies cited in the package insert, and

   g. When available, hazard identification information from SDSs provided by the manufacturer.

2. Two-Part Approach to Evaluate Screened Drugs for Potential Hazards[35]

   a. Toxicity Criteria

      NIOSH evaluates information from humans[36] and animals[37] using the toxicity criteria in Section V.C.3 (Step 3) for determining whether a drug exhibits one of the toxicities set out in the NIOSH definition of a hazardous drug.

      i. For genotoxicity, relevant information from in vitro systems is also included in the evaluation.[38]

      ii. Although human data are generally preferable to animal or in vitro data for in-

[30] *See* **https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/**.

[31] NTP [2021]. 15th report on carcinogens. Research Triangle Park, NC: U.S. Department of Health and Human Services. *See* **https://ntp.niehs.nih.gov/pubhealth/roc/index-1.html#toc1**.

[32] IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Lyon, France. *See* **http://monographs.iarc.fr/ENG/Classification/index.php**.

[33] For available NTP Monographs, see **http://ntp.niehs.nih.gov/pubhealth/hat/noms/index.html**.

[34] *See* **https://ntp.niehs.nih.gov/go/ohathandbook**.

[35] Only screened drugs that might exhibit at least one of the toxicity criteria in the NIOSH definition of hazardous drug undergo a full evaluation.

[36] In evaluating human studies, the following questions are reviewed: (1) Has a plausible association been established between exposure to the drug and an adverse health effect? (2) Is there a temporal relation consistent with cause and effect? (3) What is the strength of the association? (4) Is there evidence of an exposure—adverse health effect association?

[37] In evaluating animal studies, the following questions are reviewed: (1) Are there multiple independent studies with consistent results? (2) Is there site concordance across species and/or structural analogs? (3) Are there multiple observations by sex, species, and sites? (4) Is there a progression in severity and/or type of lesions with increased exposure or dose? (5) Are the routes of exposure relevant to the human experience?

[38] Environmental Protection Agency (EPA) [1986]. Guidelines for mutagenicity risk assessment. *See* **https://www.epa.gov/risk/guidelines-mutagenicity-risk-assessment**.

dicating potential adverse health effects, NIOSH carefully considers all relevant data in its evaluation of screened drugs.

b. Molecular Properties

NIOSH evaluates whether the molecular properties of a drug may limit the potential for adverse health effects in healthcare workers exposed to the hazardous drug.

3. Toxicity Criteria

a. Carcinogenicity

i. Drug Package Insert

A finding of carcinogenicity in the prescribing information of the drug package insert generally supports a NIOSH finding of carcinogenicity.

ii. Safety Data Sheet (SDS)

A report of carcinogenicity in an SDS generally supports a NIOSH finding of carcinogenicity.

iii. Authoritative Sources

A finding of carcinogenicity from any one of the following sources generally supports a NIOSH finding of carcinogenicity.

(a) NTP Report on Carcinogens ("known to be human carcinogen" or "reasonably anticipated to be a human carcinogen")[39] or

(b) IARC ("Group 1 carcinogenic or Group 2A probably carcinogenic" or "Group 2B possibly carcinogenic").[40]

iv. Human Studies

A finding of human carcinogenicity in published peer-reviewed scientific literature generally supports a finding of carcinogenicity.

v. Animal Studies

(a) NIOSH will assess animal studies found in any of the sources described in Section V.C.1 (Step 3) and consider the evidence of carcinogenicity, including whether tumors are reported in more than one animal species and sex.

(b) Tumors in multiple organs, tumors that are not rodent-specific, and high incidence of a single tumor type in one species or sex are positive findings that generally support a NIOSH finding of carcinogenicity.

(c) Adverse effects that occur near, at, or below the maximum recommended human dose (MRHD) generally support a NIOSH finding of carcinogenicity.

b. Developmental Toxicity

[39] *See* **https://ntp.niehs.nih.gov/pubhealth/roc/index-1.html**.
[40] *See* **https://monographs.iarc.fr/list-of-classifications-volumes/**.

i. Drug Package Insert

A finding of developmental toxicity in humans in the drug package insert generally supports a NIOSH finding of developmental toxicity.

ii. SDS or Peer-Reviewed Scientific Literature

A finding of developmental toxicity in an SDS or published, peer-reviewed scientific literature generally supports a NIOSH finding of developmental toxicity.

iii. NTP

A conclusion of "serious concern for adverse effects" or "concern for adverse effects" or "some concern for adverse effects" by the NTP that human development might be adversely affected by exposure generally supports a NIOSH finding of developmental toxicity.

iv. Animal Studies

(a) Studies found in any of the sources described in Section V.C.1 (Step 3) report developmental toxicity generally support a positive finding for developmental toxicity. [41]

(b) Adverse effects that occur near, at, or below MRHD generally support a NIOSH finding of developmental toxicity.

c. Reproductive Toxicity

i. Drug Package Insert

A positive finding of reproductive toxicity in humans generally supports a NIOSH finding of reproductive toxicity.

ii. SDS or Peer-Reviewed Scientific Literature

A finding of reproductive toxicity in an SDS or in published, reviewed scientific literature generally supports a NIOSH finding of reproductive toxicity.

iii. NTP

A conclusion by the NTP of "serious concern for adverse effects," or "concern for adverse effects," or "some concern for adverse effects" on human reproduction generally supports a NIOSH finding of reproductive toxicity.

iv. Animal Studies

(a) Studies found in any of the sources described in Section V.C.1 (Step 3) that report reproductive toxicity generally support a NIOSH finding of reproductive toxicity.

(b) Adverse effects that occur near, at, or below the MRHD generally support a NIOSH finding of reproductive toxicity.

d. Organ Toxicity at Low Doses

[41]However, effects on the fetus only in the presence of maternal toxicity do not generally support a NIOSH finding of teratogenicity or other developmental toxicity. Some substances cause developmental effects only at a dose level that is maternally toxic (Kera KS [1985]. Maternal toxicity: a possible etiological factor in embryo-fetal deaths and fetal malformations of rodent-rabbit species. Teratology *31*(1):129–153). This supports the conclusion that developmental effects are secondary to maternal toxicity, thereby decreasing the significance of fetal toxicity in the presence of signs of maternal toxicity. *See* Chahoud I, Ligensa A, Dietzel L, Faqi AS [1999]. Correlation between maternal toxicity and embryo/fetal effects. Reprod Toxicol *13*:375–381.

i. Human Studies

Studies found in any of the sources described in Section V.C.1 (Step 3) that report organ toxicity at a daily therapeutic dose less than or equal to 10 milligrams per day (mg/day) generally support a NIOSH finding of organ toxicity at low doses.[42]

ii. Animal Studies

Studies found in any of the sources described in Section V.C.1 (Step 3) that report serious organ toxicity in animal models at doses less than 1 milligram per kilogram per day (mg/kg/day) generally support a NIOSH finding of organ toxicity at low doses.

e. Genotoxicity

i. Human Studies

Human genotoxicity studies are not commonly available for evaluation. If available, NIOSH gives preference to human genotoxicity studies over animal and in vitro studies. However, NIOSH considers all relevant information in its evaluation.

ii. Animal Studies

(a) Studies found in any of the sources described in Section V.C.1 (Step 3) that report genotoxicity in laboratory animals generally support a NIOSH finding of genotoxicity.

(b) Generally, in vivo animal testing is given greater weight than in vitro testing.

iii. In Vitro Systems

(a) Positive genotoxicity results in two or more in vitro test systems reported in any of the sources described in Section V.C.1 (Step 3) generally support a NIOSH finding of genotoxicity.

(b) Consistent findings of genotoxicity among human, animal and/or in vitro systems generally support a NIOSH finding of genotoxicity.

f. Structure and Toxicity Profile that Mimics Existing Drugs Determined Hazardous

A finding that a drug is an isomer or close chemical analog of a drug that meets the definition of a hazardous drug generally supports including it on the *List*. This criterion is typically used when toxicity information specific to the drug under evaluation is insufficient to evaluate whether it meets the definition of a hazardous drug.

4. Molecular Properties

a. Factors Considered in Assessing Molecular Properties

The molecular properties of a drug may limit the potential mechanism of toxicity or limit the relevant routes of exposure of a drug.[43] An assessment that the molecular properties of a drug may limit the potential for adverse health effects in healthcare workers supports a NIOSH finding that the drug does not meet the criteria in the NIOSH definition of a hazardous drug.

[42] *See supra* note 16.

[43] For example, very large drug molecules may be therapeutically active and potentially toxic when injected, but may be too large to be absorbed appreciably through inhalation, ingestion, dermal, or percutaneous (needle puncture) routes of exposure.

b. Factors Not Considered in Assessing Molecular Properties

NIOSH does not consider dosage form as a molecular property of a drug because the same active pharmaceutical product can be offered in several different dosage forms, new dosage forms can be offered later, and some dosage forms can be discontinued.

5. Integrated Toxicity and Molecular Properties Hazard Assessment

NIOSH considers the toxicity and molecular properties ("integrated assessment") of a hazardous drug when making a determination if the drug meets the NIOSH definition of a hazardous drug.

6. Evaluation Outcomes

a. Not Proposed for Placement on the *List*

Evaluated drugs are not proposed for placement on the *List* when the integrated assessment does not support a NIOSH determination that the drug meets the NIOSH definition of a hazardous drug.

b. Proposed for Placement on the *List*

Evaluated drugs are proposed for placement on the *List* when the integrated assessment supports a NIOSH determination that the drug meets the NIOSH definition of a hazardous drug.

7. Tabular Arrangement of Hazardous Drugs on the *List*[44]

a. Table 1 contains drugs that have MSHI in the package insert and/or meet the NIOSH definition of a hazardous drug and one or more of these criteria:

i. Are classified by the NTP as "known to be a human carcinogen," and

ii. Are classified by the IARC as Group 1 "carcinogenic to humans" or Group 2A "probably carcinogenic to humans."

b. Table 2 contains drugs that meet the NIOSH definition of a hazardous drug and

i. Do not have MSHI,

ii. Are not classified by the NTP as "known to be a human carcinogen," and

iii. Are not classified by the IARC as Group 1 "carcinogenic to humans" or Group 2A "probably carcinogenic to humans."

**D. Step 4: Peer Review of Potentially Hazardous Drugs**

Consistent with the Office of Management and Budget's Information Quality Guidelines,[45] NIOSH conducts peer review examining NIOSH's approach to identifying, screening, evaluating, and placing a drug on, moving a drug within, or removing a drug from the *List*. Particular emphasis in the peer review is placed on the integrated hazard assessment and the applicability of the decision criteria. After peer review, NIOSH reexamines the decision criteria with respect to the peer review comments and reevaluates drug placement on the *List*.

[44]In addition to the two tables, each update of the *List* includes description of changes made to the *List*.

[45]Office of Management and Budget [2004]. Final information quality bulletin for peer review. Available at **https://www.govinfo.gov/content/pkg/FR-2005-01-14/pdf/05-769.pdf**.

### E. Step 5: Public Review of Potentially Hazardous Drugs

NIOSH publishes a *Federal Register* notice seeking public comment on the following four categorical determinations of the evaluated drugs and, for drugs proposed for placement on the *List*, their tabular location on the *List*:

**Category 1**—Insufficient Toxicity Information Available to Meet NIOSH Definition of Hazardous Drug

Screened drugs with insufficient information to determine whether the drug exhibits any one of the toxicity criteria found in the NIOSH definition of hazardous drug are not eligible for evaluation and are not proposed for placement on the *List* (Section V.B.2.b, Step 2).

**Category 2**—Available Information Shows a Toxic Effect that Does Not Meet the NIOSH Definition of a Hazardous Drug

Screened drugs with available toxicity information showing a toxic effect that does not meet the NIOSH definition of hazardous drug are not proposed for placement on the *List* (Section V.B.2.c, Step 2).

**Category 3**—Available Toxicity Information Does Not Support a Determination that the Drug Meets the NIOSH Definition of a Hazardous Drug

Evaluated drugs are not proposed for placement on the *List* when toxicity and molecular properties assessment does not support a NIOSH determination that the drug meets the NIOSH definition of a hazardous drug (Section V.C.6.a, Step 3).

**Category 4**—Available Toxicity and Molecular Properties Assessment Supports a Determination that the Drug Meets the NIOSH Definition of a Hazardous Drug

Evaluated drugs are proposed for placement on the *List* when toxicity and molecular properties assessment supports a determination that the drug meets the NIOSH definition of a hazardous drug (Section V.C.6.b, Step 3).

### F. Step 6: Placement of Hazardous Drugs on the *List* and in Tables

1. After consideration of peer review and public comments, the NIOSH Director will make a final determination on whether to place an evaluated drug on the *List* and determine the tabular location of the drug on the *List*.

2. NIOSH will publish the updated *List*, available through the **NIOSH Hazardous Drug Exposures in Healthcare** website,[28] and announce the availability of the updated *List* in a *Federal Register* notice.

## VI. Request for a NIOSH Reevaluation

### A. Request

A request by a party asking NIOSH to reevaluate its determination to place, or not to place, a drug on the *List*, or a decision to place a drug on a particular table of the *List*, must

1. Be submitted in writing as a letter to the NIOSH Director,[46] including a letter summarizing the request,[47] and

[46]Requests can be submitted to the following address: NIOSH, 395 E Street, S.W., Suite 9200, Washington, D.C. 20201.

[47]The requestor should prepare a letter keeping in mind that NIOSH will publish the letter for public view. *See* Section VI.B.3. NIOSH will maintain the confidentiality of any proprietary and/or trade secret information provided to NIOSH to the full extent it is permitted to do so under the Federal Trade Secret Act, 18 USC § 1905, and the Freedom of Information Act, 5 USC § 552 (FOIA). NIOSH will maintain personally identifiable information in accordance with the Privacy Act of 1974, 5 USC § 552a.

2. Present new scientific information that is relevant to the issue of whether the drug does or does not meet the NIOSH definition of a hazardous drug or a decision to place a drug on a particular table of the *List*.

   **Note:** If the request for a reevaluation does not contain new scientific information, the request will not be considered a valid request for a NIOSH reevaluation.

**B. Initial NIOSH Evaluation of a Request for a Reevaluation**

After receipt of a request for a reevaluation, NIOSH will

1. Determine if the request meets the requirements in Section VI.A,

2. Notify the requestor by letter of the decision whether the request meets the requirements of Section VI.A, and

3. Following initial examination of a reevaluation request, publish the letter requesting the reevaluation review, and NIOSH's response to the request, accessible through the **NIOSH Hazardous Drug Exposures in Healthcare** website.[28]

**C. NIOSH Review of Evidence Presented in the Request for a Reevaluation**

If NIOSH determines that the request meets the requirements in Section VI.A, NIOSH will

1. Review all of the information NIOSH used to make its determination to place the requested drug on the *List*, or not to place the drug on the *List*, or place the drug on a particular table of the *List*, including the original identification, screening and evaluation reviews conducted by NIOSH, and all peer reviewer and public comments.

2. Review the request for a reevaluation and search for any additional hazard identification (toxicity) and hazard characterization information about the drug that is relevant to the criteria set out in the NIOSH definition of a hazardous drug.

3. Develop an initial recommendation and summary of evidence about whether to maintain or change the status of the drug subject to the reevaluation request.

**D. Peer Review of the Initial Recommendation**

NIOSH will conduct peer review consistent with the Office of Management and Budget's Information Quality Guidelines[48] of its reevaluation recommendation on whether to maintain or change the status of the drug subject to the review request.

**E. Public Comment on the Initial Recommendation**

NIOSH will solicit public comments on the initial recommendation to maintain or change the status of the drug subject to the reevaluation request in a *Federal Register* notice with a public comment period of 30 days.

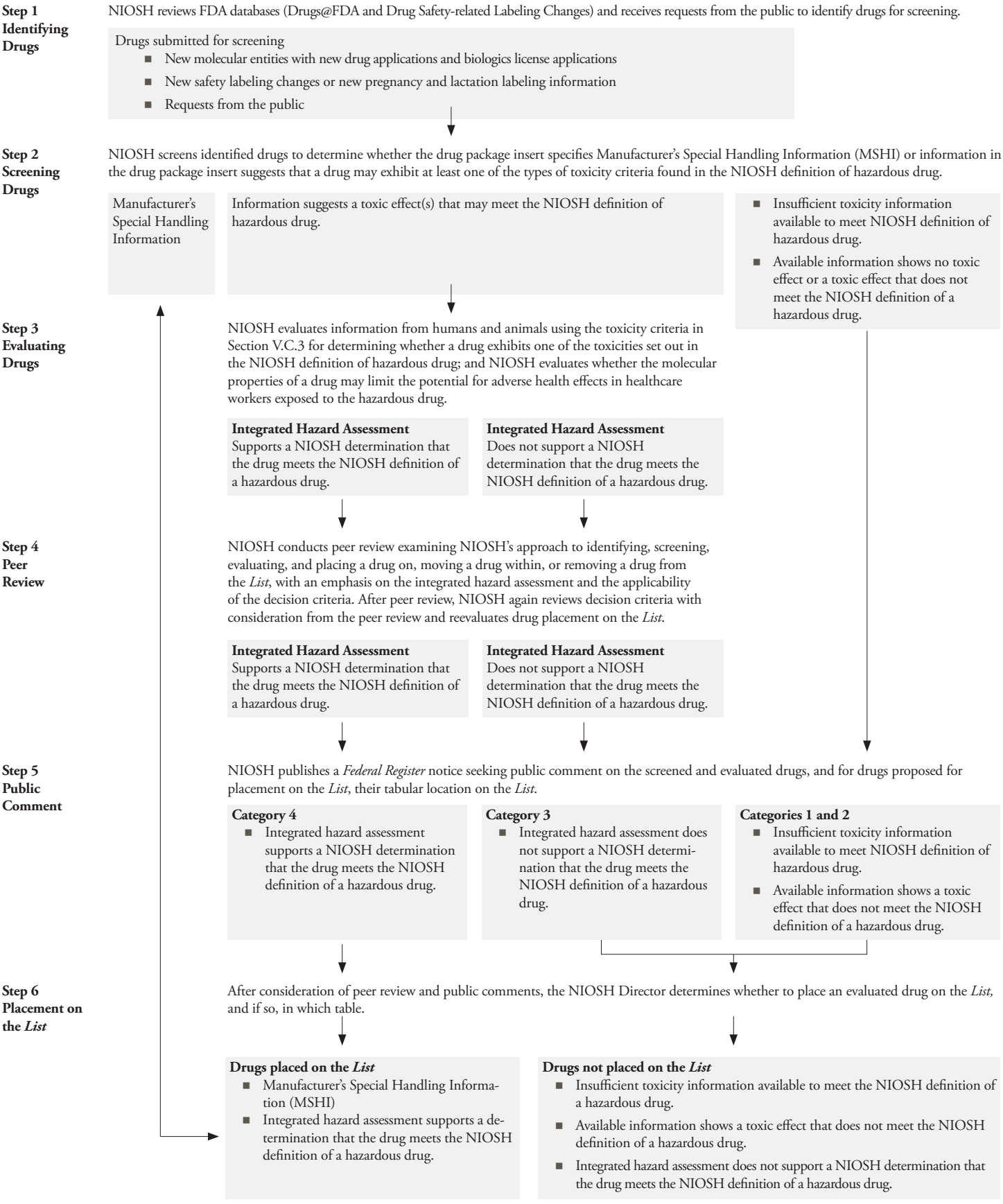
[48] *See supra* note 45.

**F. Final Reevaluation Determination**

1. After consideration of peer review and public comments, NIOSH will make a final reevaluation determination and inform the requestor by letter of the final reevaluation determination.

2. NIOSH will publish the final reevaluation determination in a *Federal Register* notice, and on the **NIOSH Hazardous Drug Exposures in Healthcare** website.[28] If appropriate, NIOSH will make a change to the status of the drug subject to the reevaluation (e.g., remove, add, or move) in the next update of the *List*.

## Figure 1. Identifying, Screening, Evaluating, and Reviewing Drugs for Placement on the *List*



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