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Policy and Procedures for Developing the NIOSH List of Antineoplastic and Other Hazardous Drugs In Healthcare Settings

Draft: February 9, 2018

I. Authority

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

II. Purpose

The *Policy and Procedures for Developing the NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings* is intended to describe the methodology the National Institute for Occupational Safety and Health (NIOSH) uses to determine whether a drug meets the NIOSH definition of a hazardous drug. Drugs that meet the NIOSH definition of a hazardous drug are placed on the *List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings ("List*").

III. Background

In 2004, NIOSH published an Alert entitled *Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings* ("*Alert*").[2] The *Alert* contained a sample list of drugs identified by NIOSH as hazardous to workers in healthcare settings. Since 2010, NIOSH has updated the NIOSH *List* every two years.[3] The biennial *List* is subdivided into three tables: Table 1 contains antineoplastic drugs, including those with special handling information

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[1] 29 U.S.C. § 651 *et seq.*

[2] NIOSH [2004]. 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, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2004-165.

[3] NIOSH [2010]. NIOSH list of antineoplastic and other hazardous drugs in healthcare settings, 2010. Cincinnati, OH: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health. DHHS (NIOSH). Publication No. 2010-167; NIOSH [2012]. NIOSH list of antineoplastic and other hazardous drugs in healthcare settings, 2012. By Connor TH, MacKenzie BA, DeBord DG, Trout DB, O'Callaghan JP. Cincinnati, OH: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health. DHHS (NIOSH) Publication No. 2012-150; NIOSH [2014]. NIOSH list of antineoplastic and other hazardous drugs in healthcare settings, 2014. By Connor TH, MacKenzie BA, DeBord DG, Trout DB, O'Callaghan JP. Cincinnati, OH: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health. DHHS (NIOSH) Publication No. 2014-138; and NIOSH [2016]. NIOSH list of antineoplastic and other hazardous drugs in healthcare settings, 2016. By Connor TH, MacKenzie BA, DeBord DG, Trout DB, O'Callaghan JP. Cincinnati, OH: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health. DHHS (NIOSH) Publication No. 2016-161.

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provided by the manufacturer;[4] Table 2 contains non-antineoplastic drugs, including those with special handling information; and Table 3 contains non-antineoplastic drugs that primarily have adverse reproductive effects.

The NIOSH *Alert* and *List* is designed to assist employers in providing safe and healthy workplaces by educating employers and workers alike about the potential health risks associated with handling U.S. Food and Drug Administration ("FDA")-approved drugs identified by NIOSH as hazardous drugs in healthcare settings. The *Alert* and the *List* create no legal obligation for employers; they are advisory in nature and informational in content.

IV. Scientific Approach

A. Evidence of Adverse Health Effects in Workers from Handling Patient Drugs

The potential beneficial effect of a drug to a patient frequently outweighs the risks of its use. A worker occupationally exposed to the same drug obtains no therapeutic benefit from the drug, but may experience adverse health effects nonetheless. Scientific evidence indicates that the adverse health effects seen in patients undergoing drug treatment are often similar to those observed in workers occupationally exposed to the same drug.

Workers occupationally exposed to drugs used in healthcare settings may experience various adverse health effects, including (1) acute health effects, such as skin rashes, and mucous membrane irritation;[5] (2) chronic health effects, including cancer;[6] and (3) adverse reproductive events, such as infertility, spontaneous abortions, and congenital malformations.[7] Even though workers in healthcare settings experience smaller individual doses of a drug through occupational exposure than do patients undergoing

[4] 21 C.F.R. § 201.57(c)(17)(iv).

[5] Eisenberg S [2009]. Safe handling and administration of antineoplastic chemotherapy. J Infus Nurs 32(1):23–32; Massoomi F, Neff B, Pick A, Daneskas P [2008]. Implementation of a safety program for handling hazardous drugs in a community hospital. Am J Heath-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.

[6] Suspiro A, Prista J [2011]. Biomarkers of occupational exposure do [*sic*] anticancer agents: a minireview. Toxicol Lett 207:42-542; 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; 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.

[7] 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; Connor TH, Lawson CC, Polowich 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; 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.

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medical treatment, workers may experience repeated exposure to a single hazardous drug, or repeated exposure to combinations of hazardous drugs, over a longer period of time.

Thus, the drug safety information generated by manufacturers, and submitted in a new drug application to the FDA, is an important source of information that can be useful not only for a patient, but also for the protection of workers from the potential adverse health effects associated with the handling of hazardous drugs in healthcare settings.

B. Systematic and Sequential Methodology

NIOSH uses a systematic and sequential approach for assessing and interpreting scientific data and other information in order to determine whether an FDA-approved drug meets the NIOSH definition of a hazardous drug. NIOSH's systematic approach to evaluating the hazard potential of a drug includes: (1) reviewing FDA databases to identify drugs that have the potential to meet the NIOSH definition of hazardous drug; (2) reviewing pre-clinical and clinical information provided by manufacturers, and other published sources, to identify information relevant to making a determination about placing a drug on the *List*; (3) assessing, integrating and synthesizing evidence from human, animal, and *in vitro* studies of drug toxicity; (4) using pre-established, toxicity evaluation criteria in making a decision to place a drug on the *List*; and (5) allowing for reconsideration of a NIOSH decision to place a drug on the *List,* or not to place a drug on the *List*.

The *Policy and Procedures for Developing the NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings* is not intended to constrain NIOSH judgement such that strict adherence could lead to assessments that do not represent current scientific thinking or are not suitable for the range of factors that need to be considered when reviewing an individual drug. NIOSH expects to update this *Policy and Procedures* as new science emerges or NIOSH experience indicates that a revision is appropriate.

C. Hazardous Drug Identification

The identification of a hazardous drug, predicated on whether the intrinsic properties of a drug meet the types of toxicity described in the NIOSH definition of hazardous drug, is the first step in assessing the risk to workers handling hazardous drugs. NIOSH evaluates new molecular entities with new drug applications and biologics license applications, and new safety labeling changes for the two-year period following the previous update of the *List* using specific criteria to identify if a drug is hazardous.

The *Alert* and *List* do not represent, and cannot provide, site-specific risk assessment or risk management information about hazardous drugs. The risk of an adverse health

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effect to a worker handling a drug identified on the *List* depends on exposure factors unique to a particular work setting. Such factors include, but are not limited to, the following: (1) the dosage form of the drug;[8] (2) the route of exposure; (3) the frequency, duration, and magnitude of exposure; (4) work practices; and (5) the presence or absence of any exposure controls, such as engineering controls or personal protective equipment.

Worker activities in healthcare settings that can potentially result in exposure to hazardous drugs include receipt, storage, preparation, compounding or similar manipulation, dispensing, transporting, administration, and other patient care activities, spill cleanup, and transport or disposal of drugs and patient waste. Potential routes of worker exposure to hazardous drugs include dermal absorption, inhalation, ingestion, and percutaneous injury.[9]

NIOSH encourages each healthcare workplace to create its own list of hazardous drugs based on drugs included in its formulary, the risk factors identified above, as well as the types of toxicity described in Section VII.C.3.a. through C.3.f. The NIOSH *Lis*t is only one of several tools employers can use to protect workers in healthcare settings from exposure to hazardous drugs. NIOSH encourages employers to review all available approaches to protecting workers in healthcare settings from occupational exposure to hazardous drugs, and to implement those measures that will effectively protect workers in their workplace.[10]

V. Application

The NIOSH *Alert* and the *List* provide information for workers and employers about handling hazardous drugs in healthcare settings, veterinary care settings, drug research laboratories, community pharmacies, and home healthcare agencies. Occupational groups in these settings include pharmacy personnel, nursing personnel, physicians, physician assistants, operating room personnel, environmental services workers, research laboratorians, veterinary care workers, and shipping/receiving personnel.

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[8] See Drugs@FDA Glossary of Terms at https://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm. ("A dosage form is the physical form in which a drug is produced and dispensed, such as a tablet, a capsule, or an injectable.")

[9] NIOSH [2004]. 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, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2004-165.

[10] Badry N, Fabbro J, de Lemos ML [2014]. Hazards in determining whether a drug is hazardous. J Oncol Pharm Pract 20:312-315; Chaffee BW, Armistead JA, Benjamin BE, Cotugno MC, Forrey RA, Hintzen BL, Pfeiffenberger T, Stevenson JG [2010]. Guidelines for the safe handling of hazardous drugs: consensus recommendations. Am J Health-Sys Pharm 67:1545-1546; Kaestli L-Z, Fonzo-Christe C, Bonfillon C, Desmeules J, Bonnabry P [2013]. Development of a standardized method to recommend protective measures to handle hazardous drugs in hospitals. Eur J Hosp Pharm 20:100-105.

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The *Alert* and *List* are not intended for use by workers handling drugs during pharmaceutical manufacturing, or workers handling "vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins."[11]

VI. Definitions

A. Drug

For the purposes of the *Alert* and *List*, NIOSH adopts the FDA definition of "drug." According to the FDA, a "drug is defined as:

- A substance recognized by an official pharmacopoeia or formulary.
- A substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease.
- A substance (other than food) intended to affect the structure or 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.
- Biological products are included within this definition and are generally covered by the same laws and regulations, but differences exist regarding their manufacturing processes (chemical process versus biological process)."[12]

B. Hazardous Drug

NIOSH defines a 'hazardous drug' as a drug that is:

1. Approved for use in humans[13] by the FDA;[14]
2. Not otherwise regulated by the U.S. Nuclear Regulatory Commission;[15] and
3. Either:

[11] See Drugs@FDA Glossary of Terms at https://www.fda.gov/drugs/informationondrugs/ucm079436.htm#D.
[12] See Drugs@FDA Glossary of Terms at https://www.fda.gov/drugs/informationondrugs/ucm079436.htm#D.
[13] Although only drugs approved by the 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.
[14] 21 U.S.C. § 301 *et seq*.
[15] 10 C.F.R. 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*.

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a. Accompanied by prescribing information in the "package insert"[16] that includes special handling information to protect workers handling the drug, or

b. Exhibits one of more of the following types of toxicity in humans, animal models, or *in vitro* systems: carcinogenicity; teratogenicity or other developmental toxicity; reproductive toxicity; organ toxicity at low doses;[17] genotoxicity; or structure and toxicity profile that mimics existing drugs determined hazardous by exhibiting any one of the previous five toxicity types.[18]

VII. Identifying, Screening, Evaluating, and Reviewing a Drug for Placement on the *List*[19]

A. Identifying Potentially Hazardous Drugs (Step 1)

1. Each month, NIOSH reviews the following FDA databases to identify drugs to be screened and evaluated for placement on the *List*:

[16] 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 the 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."

[17] 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 mg/ day or a dose of 1 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 µg/m3 after applying appropriate uncertainty factors [Sargent and Kirk 1988; Naumann and Sargent 1997; Sargent et al. 2002]. OELs in this range are typically established for potent or toxic drugs in the pharmaceutical industry. Under all circumstances, an evaluation of all available data should be conducted to protect health care workers.

[18] NIOSH [2004]. 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, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2004-165.

[19] See Figure 1 for NIOSH Procedures for Identifying, Screening, Evaluating, and Reviewing a Drug for Placement on the List.

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a. *Drugs@FDA: FDA Approved Drug Products* by month.[20] This FDA database lists new molecular entities (NME)[21] with new drug applications[22] and biologics license applications.[23]

b. *Drug Safety Labeling Changes*.[24] This FDA database identifies drugs with new safety labeling changes (new boxed warnings,[25] and/or warnings and precautions) or new pregnancy and lactation labeling information.[26]

2. NIOSH may also receive a request from an interested party to add a drug to the *List*. Requests to add a drug must be submitted in writing to the NIOSH Director. The request must include information that supports a decision that the drug meets the NIOSH definition of hazardous drug.

B. Screening Potentially Hazardous Drugs (Step 2)

1. Identified drugs are screened to determine:

a. Whether the drug package insert specifies special handling information to protect workers handling the drug; or

b. Whether information in the drug package insert suggests that a drug may exhibit at least one of the types of toxicity found in the NIOSH definition of hazardous drug.

2. Although the *entire* drug package insert is examined, the following specific sections may indicate that the drug exhibits at least one of the types of toxicity found in the NIOSH definition of hazardous drug:[27]

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

[21] 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.")

[22] 21 C.F.R. Part 314.

[23] 21 C.F.R. Part 601.

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

[25] 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."

[26] 21 C.F.R. § 201.57(c)(9)(i) and (ii) and 21 § C.F.R. 201.80.

[27] The package inserts for drug approved prior to FDA's drug labeling regulations may not include these specific numbered sections although the same type of content is included. See 21 C.F.R. § 201.56(b)(1) and 201.80.

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a. Section 1: Box warning, if available;[28]

b. Section 5: Warnings and Precautions (any organ toxicity, carcinogenicity, or embryo-fetal toxicity);[29]

c. Section 6: Adverse Reactions (any post-marketing experience reported by the manufacturer);[30]

d. Section 8: Use in Special Populations (pregnancy information, any human or animal development toxicity);[31]

e. Section 13: Non-clinical toxicology (animal data on carcinogenesis, mutagenesis and impairment of fertility);[32]

f. Section 15: References, if available;[33] and

g. Section 16: Storage and Handling, if available (special handling or disposal information for workers).[34]

3. Screening (Step 2) Outcomes

a. Special Handling Information

If a manufacturer provides special handling information to protect workers handling the drug, then NIOSH will make the special handling information available on the hazardous drug topic page of the NIOSH website,[35] and propose to place the drug on the *List.* Go to Section VII.E.1.a. (Step 5).

b. Insufficient Toxicity Information Available to Meet NIOSH Definition of Hazardous Drug

If there is insufficient information to suggest that the drug exhibits any one of the types of toxicity found in the NIOSH definition of hazardous

[28] 21 C.F.R. § 201.57(c)(1).
[29] 21 C.F.R. § 201.57(c)(6).
[30] 21 C.F.R. § 201.57(c)(7).
[31] 21 C.F.R. § 201.57(c)(9).
[32] 21 C.F.R. § 201.57(c)(14).
[33] 21 C.F.R. § 201.57(c)(16).
[34] 21 C.F.R. § 201.57(c)(17).
[35] See https://www.cdc.gov/niosh/topics/hazdrug/default.htm.

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drug, then NIOSH will not propose to add the drug to the *List*. Go to Section VII.E.1.b. (Step 5).

c. Available Information Shows No Toxic Effect or Shows a Toxic Effect that Does Not Meet the NIOSH Definition of a Hazardous Drug

If information shows no toxic effect or shows a toxic effect that does not meet NIOSH definition of hazardous drug, then NIOSH will not propose to add the drug to the *List*. Go to Section VII. E.1.c. (Step 5).

d. Available Information Suggests Toxic Effect

If, after screening a drug, available information suggests a toxic effect that does meet the NIOSH definition of hazardous drug, then NIOSH will evaluate the drug to determine if it will propose, or not propose, to add the drug to the *List*. Go to Section VII.C. (Step 3).

C. Evaluating Potentially Hazardous Drugs (Step 3)

1. Sources of Information for Evaluating Screened Drugs

NIOSH may consult the following sources of information to evaluate each screened drug that might exhibit at least one of the types of toxicity in the NIOSH definition of hazardous drug:

a. Information in the drug package insert;

b. FDA information pertaining to new drug safety labeling changes;[36]

c. When available, relevant information about carcinogenicity from:

(1) National Toxicology Program (NTP) within the U.S. Department of Health and Human Services; [37]

(2) U.S. Environmental Protection Agency (EPA);[38]

[36] See https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/.
[37] NTP (National Toxicology Program, DHHS) [2016]. 14th report on carcinogens. Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service. See https://ntp.niehs.nih.gov/pubhealth/roc/index-1.html#toc1.
[38] EPA (Environmental Protection Agency). Integrated Risk Information System (IRIS) Assessments. See https://cfpub.epa.gov/ncea/iris2/atoz.cfm. Accessed August 14, 2017.

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(3) World Health Organization's International Agency for Research on Cancer (IARC);[39] and

(4) NIOSH.[40]

d. When available, relevant information about reproductive toxicity, teratogenicity, or developmental toxicity from the NTP Center for the Evaluation of Risks to Human Reproduction (CERHR),[41] and from its successor, the Office of Health Assessment and Translation (OHAT);[42]

e. When available, published, peer-reviewed scientific literature about the hazard potential of a particular drug, including any studies cited in the package insert that are relevant to workers in a health care setting; and

f. When available, toxicity information from Safety Data Sheets (SDSs) provided by the manufacturer.

2. Approach Used to Evaluate Screened Drugs[43]

a. NIOSH evaluates information from humans[44] and animals[45] using the criteria in Section VII.C.3. for determining whether a drug exhibits one of the types of toxicity found in the NIOSH definition of hazardous drug. For genotoxicity, the relevant information from *in vitro* systems is also included in the evaluation.[46]

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

[40] NIOSH Carcinogen List. See https://www.cdc.gov/niosh/topics/cancer/npotocca.html.

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

[42] See https://www.niehs.nih.gov/research/atniehs/dntp/assoc/ohat/index.cfm.

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

[44] 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? (5) Is it biologically plausible that the exposure causes the effect?

[45] 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?

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

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b. Although human data are generally preferable to animal or *in vitro* data for indicating potential adverse health effects, NIOSH carefully considers all relevant data in its evaluation of screened drugs.

3. Toxicity Evaluation

a. Carcinogenicity

(1) Drug Package Insert

A finding of carcinogenicity in the prescribing information of the drug package insert is determinative of a NIOSH finding[47] of carcinogenicity.

(2) Safety Data Sheet (SDS)

A report of carcinogenicity in a SDS may support a NIOSH finding[48] of carcinogenicity.

(3) Authoritative Sources

A finding of carcinogenicity from any of the following sources is supportive of a NIOSH finding of carcinogenicity.

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

(b) EPA Integrated Risk Information System ("carcinogenic to humans," "likely to be carcinogenic to humans" or "suggestive evidence of carcinogenic potential," Group A, Group B1, Group B2, or Group C);

(c) IARC (Group 1 or 2A or 2B); or

[47] Information is determinative of a NIOSH finding when the drug package insert (see Section VII.B.1.b.) indicates the relevant toxicity.

[48] Information may support a NIOSH finding when the scientific evidence, taken as a whole, demonstrates a plausible relationship between the drug being evaluated and the type of toxicity in question such that NIOSH may conclude that the drug exhibits the relevant toxic effect. Information may not support a NIOSH finding when the scientific evidence, taken as a whole, does not demonstrate a plausible relationship between the drug being evaluated and the type of toxicity in question such that NIOSH may conclude that the drug does not exhibit the relevant toxic effect.

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(d) NIOSH ("potential occupational carcinogen" or "occupational carcinogen").[49]

(4) Human Studies

A finding of human carcinogenicity in published, peer-reviewed scientific literature may support a finding of carcinogenicity.

(5) Animal Studies

(a) NIOSH will assess animal studies found in any of the sources described in Section VII.C.1. and consider the evidence of carcinogenicity, including whether tumors are documented 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. Teratogenicity and Other Developmental Toxicity

(1) Drug Package Insert

A finding of teratogenicity or developmental toxicity in humans in the drug package insert is determinative of teratogenicity or development toxicity.

(2) Peer-Reviewed Scientific Literature or SDS

A finding of reproductive toxicity in published, peer-reviewed scientific literature, or in a SDS, may support a NIOSH finding of reproductive toxicity.

(3) NTP

[49] NIOSH's evaluation of drugs for placement on the *List* may not conform to the NIOSH Chemical Carcinogen Policy. See https://www.cdc.gov/niosh/docs/2017-100/default.html.

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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 is supportive of a NIOSH finding of teratogenicity or developmental toxicity.

(4) Animal Studies

(a) Studies found in any of the sources described in Section VII.C.1. that report teratogenicity or developmental toxicity generally support a positive finding for teratogenicity or developmental toxicity.

(b) However, effects on the fetus only in the presence of maternal toxicity do not generally support a NIOSH finding of teratogenicity or developmental toxicity.[50]

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

c. Reproductive Toxicity

(1) Drug Package Insert

A positive finding of reproductive toxicity in humans is determinative of a NIOSH finding of reproductive toxicity.

(2) Peer-Reviewed Scientific Literature or SDS

A finding of reproductive toxicity in published, peer-reviewed scientific literature, or in a SDS, may support a NIOSH finding of reproductive toxicity.

(3) NTP

[50] Some substances cause developmental effects only at a dose level that is maternally toxic (Kera KS [1085] 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 Tox 13:375-381.

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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 is supportive of a NIOSH finding of reproductive toxicity.

(4) Animal Studies

(a) Studies found in any of the sources described in Section VII.C.1. 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

(1) Human Studies

Studies found in any of the sources described in Section VII.C.1. that report organ toxicity at a daily therapeutic dose less than or equal to 10 mg/day, supports a NIOSH finding of organ toxicity at low doses.

(2) Animal Studies

Studies found in any of the sources described in Section VII.C.1. that report serious organ toxicity in animal models at doses less than 1 mg/kg/day support a NIOSH finding of organ toxicity at low doses.

e. Genotoxicity

(1) Human Studies

Human genotoxicity studies are not commonly available for evaluation. If available, NIOSH gives preference to those studies, but considers all relevant information in its evaluation.

(2) Animal Studies

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

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

(3) *In vitro* Systems

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

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

f. Structure and Toxicity Profile

The inclusion on the *List* of isomers or close chemical analogs of the drug being evaluated is generally determinative of a NIOSH finding that the drug's structure and toxicity profile mimic a drug or drugs on the *List*.

4. Evaluation Outcomes

a. Not Proposed for Placement on the *List*

Evaluated drugs are not proposed for placement on the *List* when available toxicity information demonstrates or supports a NIOSH determination that the drug does not meet the NIOSH criteria for at least one of the types of toxicity found in the NIOSH definition of a hazardous drug. Go to Steps 4 and 5.

b. Proposed for Placement on the *List*

Evaluated drugs are proposed for placement on the *List* when available toxicity information demonstrates or supports a NIOSH determination that the drug meets the NIOSH criteria for at least one of the types of toxicity found in the NIOSH definition of a hazardous drug. Go to Steps 4 and 5.

D. Peer Review of Potentially Hazardous Drugs (Step 4)

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1. NIOSH conducts peer review of each evaluated drug that is proposed for placement on the *List*, and each evaluated drug that is not proposed for placement on the *List*, consistent with the Office of Management and Budget's Information Quality Guidelines.[51]

2. NIOSH will consider each peer review and may make a change in whether or not to propose to place a drug on the List based on a peer review. See Section VII.E.1.a. through E.1.e.

3. NIOSH will place de-identified peer reviews in the NIOSH Docket upon publication of the *Federal Register* notice required by Section VII.F.3. (Step 6).

E. Public and Stakeholder Review of Potentially Hazardous Drugs (Step 5)

1. NIOSH will publish a *Federal Register* notice seeking public comment on the following five groups of drugs:

   a. Category 1—Special Handling Information

      Screened drugs for which the manufacturer has provided special handling information for workers are proposed for placement on the *List* (see Section VII.B.3.a.).

   b. Category 2—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 types of toxicity found in the NIOSH definition of hazardous drug, are not eligible for evaluation, and are not proposed for placement on the *List* (see Section VII.B.3.b.).

   c. Category 3—Available Information Shows a Toxic Effect that Does Not Meet the NIOSH Definition of a Hazardous Drug

      Screened drugs with available information showing a toxic effect that does not meet the NIOSH definition of hazardous drug are not proposed for placement on the *List* (see Section VII.B.3.c).

[51] Office of Management and Budget. [2004]. Final information quality bulletin for peer review. See http://www.whitehouse.gov/omb/memoranda_fy2005_m05-03.

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d. Category 4—Available Toxicity Information Does Not Demonstrate or 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 available toxicity information does not demonstrate or support a NIOSH determination that the drug meets the NIOSH criteria for at least one of the types of toxicity found in the NIOSH definition of a hazardous drug (see Section VII.C.4.a.).

e. Category 5—Available Toxicity Information Demonstrates or Supports a Determination that the Drug Meets the NIOSH Definition of a Hazardous Drug

Evaluated drugs are proposed for placement on the *List* when available toxicity information demonstrates or supports a NIOSH determination that the drug meets the NIOSH criteria for at least one of the types of toxicity found in the NIOSH definition of a hazardous drug (see Section VII.C.4.b.).

2. The *Federal Register* notice will include a general explanation of the reason(s) for NIOSH's initial determination that drugs in each of the five categories are proposed for placement on the *List* or not proposed for placement on the *List*, including a synopsis of peer reviews.

3. In the *Federal Register* notice, NIOSH will solicit comments about NIOSH's initial category determinations from the public and stakeholders, such as pharmaceutical manufacturers, other Federal agencies, healthcare providers, professional organizations, and other interested parties.

4. NIOSH will provide 60 days for public comments on the *Federal Register* notice.

F. Placement of Hazardous Drugs on the *List* (Step 6)

1. After consideration of public and stakeholder comments, the NIOSH Director will make a final determination whether or not to place an identified drug on the *List.*

2. NIOSH will publish the updated *List* on the hazardous drugs topic page of the NIOSH website,[52] subdivided into three tables: Table 1 contains

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

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antineoplastic drugs, including those with a special handling information provided by the manufacturer; Table 2 contains non-antineoplastic drugs, including those with special handling information; and Table 3 contains non-antineoplastic drugs that primarily have adverse reproductive effects.

3. NIOSH announces the availability of the updated *List* in a *Federal Register* notice.

VIII. Reconsideration

A. Reconsideration of a Decision to Add a Drug to, or to Remove a Drug from, the *List*

1. NIOSH may reconsider its decision to place or not place a drug on the *List*, at its own discretion, or in response to a written request from an interested party.

2. A request from an interested party asking NIOSH to reconsider its decision to place a drug on the *List,* or a request to remove a drug from the *List,* must be submitted in writing to the NIOSH Director, and include information supporting the request.

3. Information supporting the request for reconsideration must be relevant to the issue of whether the drug does or does not meet the NIOSH definition of a hazardous drug, and present information that was not included in the *Federal Register* notice explaining the reasons to place, or not place, the drug on the *List*.

B. NIOSH Review of Reconsideration Request

After receipt of a request for reconsideration, the NIOSH Associate Director for Science (ADS) will:

1. Determine if the information supporting a request for reconsideration is new information that was not included in the determination of whether to place the drug on the *List,* and is relevant to the issue of whether the drug does or does not meet the NIOSH definition of a hazardous drug;

2. Notify the requestor by letter whether relevant information was provided; and

3. Publish the letter requesting reconsideration, and the Director's response, on the hazardous drug topic page of the NIOSH website.

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C. NIOSH ADS Review of Evidence to Place the Requested Drug on the *List* or Remove the Drug from the *List*

1. If the information provided with the request for reconsideration is information that was not included in the *Federal Register* notice explaining the NIOSH decision to place or not to place the drug on the *List,* and is relevant to the issue of whether the drug does or does not meet the NIOSH definition of a hazardous drug, the NIOSH ADS will:

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

    b. Conduct a literature search for new scientific evidence about the potential toxicity of the drug, or a lack of toxicity of the drug, that is relevant to the NIOSH definition of hazardous drug;

    c. Obtain any available safety evaluation studies the drug manufacturer may have submitted to FDA that are relevant to the NIOSH definition of hazardous drug, and, if obtained, take measures to protect from public disclosure all business confidential information provided by the manufacturer to NIOSH; and

    d. Develop a recommendation and summary of evidence for the NIOSH Director's initial determination whether to propose placement of the drug on the *List,* or to propose removal of a drug from the *List*.

2. If the NIOSH ADS concludes that the requested drug should be placed on the *List,* or be removed from the *List*, the NIOSH ADS will conduct peer review consistent with the Office of Management and Budget's Information Quality Guidelines;[53] and

3. After obtaining, reviewing and considering peer reviews, the NIOSH ADS will provide the NIOSH Director with a recommendation, and a summary of the evidence supporting the recommendation to place a drug on the *List* or to remove a drug from the *List*.

D. Initial and Final Determination by the NIOSH Director

[53] Office of Management and Budget. [2004]. Final information quality bulletin for peer review. See http://www.whitehouse.gov/omb/memoranda_fy2005_m05-03.

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1. The NIOSH Director will review the ADS recommendation and evidence summary, and make an initial determination whether to add the drug to the *List*, or to remove the drug from the *List*, or to propose another appropriate resolution to the request.

2. After the NIOSH Director makes an initial determination, the NIOSH ADS will solicit public and stakeholder comments on the Director's initial determination to add the drug to the *List*, or to remove the drug from the *List*, or propose another appropriate resolution to the request, in a *Federal Register* notice with a public comment period of 30 days.

3. After consideration of public and stakeholder comments, the NIOSH Director will make a final determination and inform the requestor of the final determination by letter.

4. NIOSH will publish the Director's final determination in *Federal Register* notice, and on the hazardous drug topic page of the NIOSH website.[54] If appropriate, NIOSH will make a change (remove or add) to the next update of the *List*.

Issued: February 9, 2018 (Draft)

[54] See https://www.cdc.gov/niosh/docket/default.html.

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Figure 1. NIOSH Procedures for Identifying, Screening, Evaluating, and Reviewing a Drug for Placement on the List