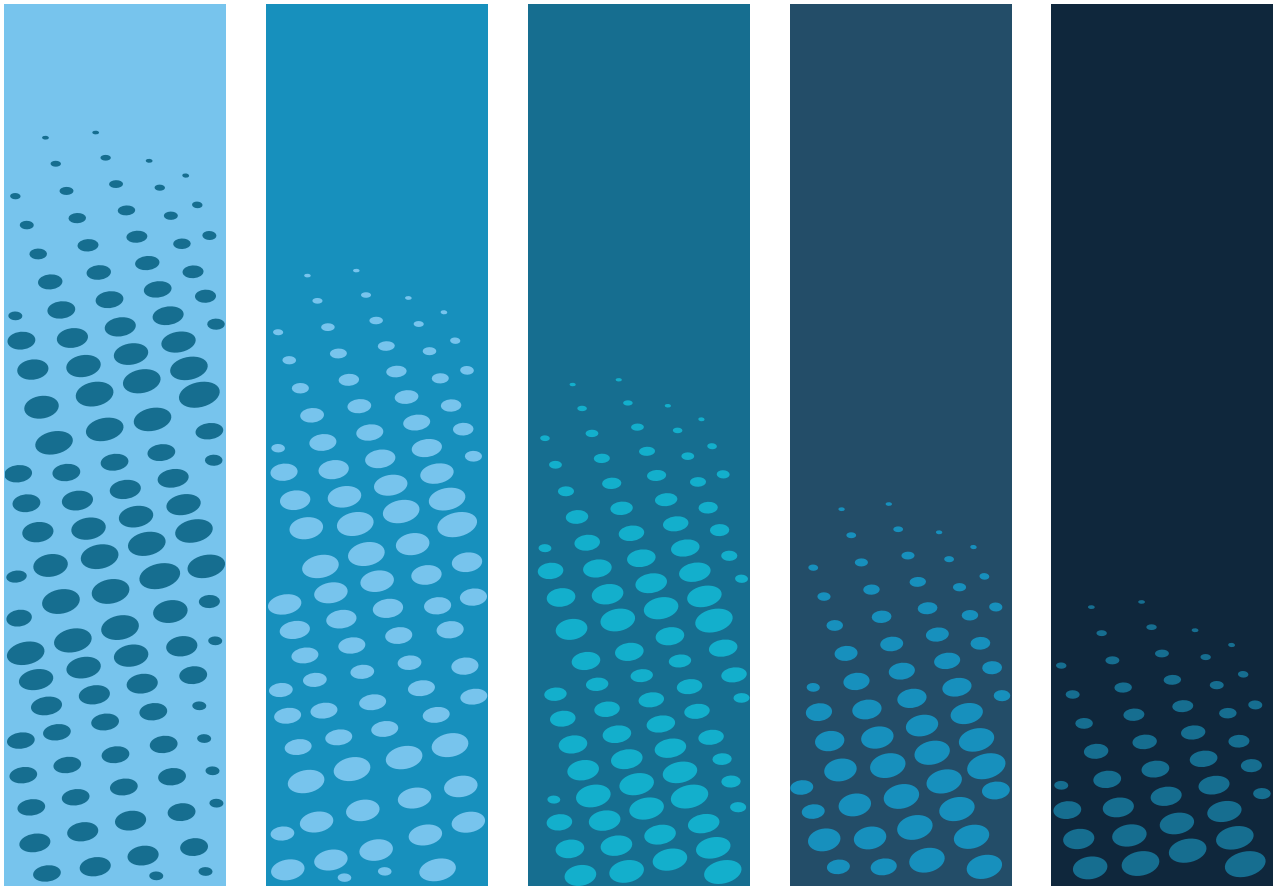
TECHNICAL REPORT

The NIOSH Occupational Exposure Banding Process for Chemical Risk Management



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Technical Report

The NIOSH Occupational Exposure Banding Process for Chemical Risk Management

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

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Foreword

A vast number of chemical substances in commerce do not have occupational exposure limits (OELs). Consequently, workers may be exposed to these substances at levels that could be harmful. OELs are a central component of occupational safety and health programs because they serve as indicators of hazards and triggers for implementing control strategies. In the absence of OELs, it is possible to use an approach known as occupational exposure banding. Occupational exposure banding is a process for quickly and accurately assigning chemical substances into categories or "bands" based on their associated health outcomes and on potency considerations.

The National Institute for Occupational Safety and Health (NIOSH) occupational exposure banding process is not meant to replace OELs; rather, it is a starting point to inform risk management decisions for controlling chemical substances that do not have OELs. This is a long-awaited resource on hazard and potency information that can serve as the foundation for making exposure-control decisions. Public health agencies, practicing occupational health and safety professionals, employers, trade associations, labor organizations, and state-level programs may share an interest in using this process to protect workers from occupational exposures, injuries, and illnesses. This document fully details the use and application of the NIOSH occupational exposure banding process and provides a summary of efforts taken to evaluate its effectiveness and usability.

John Howard, MD
Director, National Institute for Occupational Safety and Health
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Executive Summary

Occupational exposure limits (OELs) play a critical role in protecting workers and emergency response personnel from exposure to dangerous concentrations of hazardous materials [Cook 1987; Deveau et al. 2015; Paustenbach 1998; Nikfar and Malekirad 2014; Schulte et al. 2010; Skowroń and Czerczak 2015]. In the absence of an OEL, determining the appropriate controls needed to protect workers from chemical exposures can be challenging. According to the U.S. Environmental Protection Agency (US EPA), the Toxic Substances Control Act (TSCA) Chemical Substance Inventory currently contains over 85,000 chemicals that are commercially available [US EPA 2015], yet only about 1,000 of these have been assigned an authoritative (government, consensus, or peer reviewed) OEL. Furthermore, the rate at which new chemical substances are being introduced into commerce significantly outpaces OEL development, creating a need for guidance on thousands of chemical substances that lack reliable exposure limits [OSHA 2014].

To protect worker health in the absence of an OEL, occupational hygienists and safety professionals use a variety of tools such as safety data sheets, exposure monitoring, medical surveillance, and toxicity testing to make risk management decisions. However, one of the challenges faced by occupational hygienists and safety professionals is that despite the myriad sources of data on chemical substances, they have no decision-making framework to screen and discriminate the most relevant data when assessing chemical substances and developing exposure control guidance. Occupational exposure banding, also known as hazard banding or health hazard banding, is a systematic process that uses qualitative and quantitative hazard information on selected health-effect endpoints to identify potential exposure ranges or categories. **The National Institute for Occupational Safety and Health (NIOSH) occupational exposure banding process seeks to create a consistent and documented process with a decision logic to characterize chemical hazards so that timely, well-informed risk management decisions can be made for chemical substances that lack OELs.** Users can band a chemical manually or by using the occupational exposure banding e-Tool. Overall, this document provides the background, rationale, and instructions for the occupational exposure banding process and gives guidance for risk managers to identify control levels for chemicals without authoritative OELs.

Using hazard-based categories to communicate potential health concerns serves to signal workers and employers of the need for risk management. This concept is not new. Numerous hazard classification and category-based systems have seen extensive use in the occupational setting. Such systems are deeply embedded in occupational hygiene practice, particularly in the pharmaceutical industry [NIOSH 2009c; Naumann et al. 1996], and are also elements of well-developed, modern hazard communication programs such as the United Nations 2013 Globally Harmonized System of Classification and Labelling of Chemicals (GHS). The NIOSH occupational exposure banding process is distinguished from other hazard classification and category-based systems in several ways. The unique attributes of the NIOSH process include: (1) a three-tiered system that allows users of varying expertise to use the process; (2) determination of potential health impacts based on nine health endpoints separately; (3) hazard-based categories linked to quantitative exposure ranges; and (4) assessment of the process via extensive evaluation exercises to determine consistency of the occupational exposure banding process with OELs.

Each tier of the process has different requirements for data sufficiency, which allows a variety of stakeholders to use the process in many different situations. The most appropriate tier for banding depends on the availability and quality of the data, how it will be used, and the training and

expertise of the user. Whereas Tier 1 requires relatively little information and modest specialized training, each successive tier requires more chemical-specific data and more user expertise to successfully assign an occupational exposure band (OEB). A primary goal of Tier 1 is to give the user a quick summary of the most important health effects associated with exposure to the chemical substance of interest and to quickly identify toxic chemical substances that should be considered for substitution or elimination.

Tier 1 would likely be most appropriate when banding a large number of chemical substances and deciding which ones to prioritize for elimination or substitution. In general, Tier 1 can be used as a quick screening method and should be completed first, prior to progressing to Tier 2. NIOSH recommends always progressing to Tier 2 if user expertise and data are available, even when Tier 1 banding has been completed. Tier 2 requires the user to examine a number of publicly available databases and extract relevant toxicological and weight-of-evidence data to be used in the NIOSH banding algorithm. Tier 3 employs a critical assessment to evaluate experimental data and discern toxicological outcomes. A general overview of the entire process is in the next section, Occupational Exposure Banding at a Glance.

The NIOSH occupational exposure banding process considers the totality of the information across all of the nine standard toxicological health endpoints: (1) carcinogenicity; (2) reproductive toxicity; (3) specific target organ toxicity; (4) genotoxicity; (5) respiratory sensitization; (6) skin sensitization; (7) acute toxicity; (8) skin corrosion and irritation; and (9) eye damage/irritation. The process looks at each health endpoint separately for each chemical substance, and the endpoint bands allow the user to make judgements about which health effects are the primary concerns for workers who are exposed. This type of specificity allows users to customize their control strategies on the basis of potency of the chemical substance and the target organ/health effect. In addition, the banding process considers multiple routes of exposure (e.g., inhalation, dermal, eye, and oral) to determine the overall OEB.

Another important component of the NIOSH occupational exposure banding process is the five exposure bands. Occupational exposure banding uses limited chemical toxicity data to group chemical substances into one of five bands, ranging from A through E. These bands, or OEBs, define the range of air concentrations expected to protect worker health. Band E represents the lowest exposure concentration range recommendation, whereas band A represents the highest exposure concentration range [McKernan et al. 2016]. Users should note that throughout this document, bands that represent lower exposure ranges are assigned to more potent/toxic chemical substances than bands that represent higher exposure ranges.

One major benefit of occupational exposure banding is that the amount of time and data required to categorize a chemical substance into an OEB is far less than that required to develop an OEL. **An OEB is not meant to replace an OEL; rather, it serves as a starting point to inform risk management decisions when an OEL is not available.** An OEB can also assist with prioritizing chemical substances for which an OEL should be developed and can guide users, including enterprises of all sizes, in setting internal OEBs or ranges for controlling exposures to specific chemical substances.

The NIOSH occupational exposure banding process is one approach or tool for assessing chemical hazards and prioritizing control efforts. Occupational hygienists have several tools in their toolbox to protect and improve occupational health in the workplace. Likewise, there are several components in a comprehensive occupational safety and health program. For example, exposure

monitoring, medical surveillance, engineering controls, OELs, quantitative risk assessments, and personal protective equipment are all tools routinely used. Occupational exposure banding is an additional tool for professionals to consider. Although occupational exposure banding will not solve every problem or address every need, it will be a helpful addition to the occupational hygiene toolbox because it provides a blueprint for making risk management decisions.

NIOSH has performed evaluation exercises to assess consistency of the occupational exposure banding process with OELs. To evaluate the Tier 1 process, NIOSH compared the OELs of 606 chemical substances to the derived Tier 1 band for those chemical substances. This evaluation found that the NIOSH Tier 1 banding process resulted in a band that included the OEL or was more stringent than the OEL for 91% of chemical substances. Five iterative phases of Tier 2 reliability testing were performed to assess Tier 2 as the process evolved. These assessments involved over 130 chemical substances with OELs. Results of these evaluations show that Tier 2 OEBs are highly likely to be at least as stringent as OELs. Tier 2 OEBs include the OEL or are more stringent than the OEL for 98% of chemical substances tested.

Comparing OEBs with OELs is not an appropriate comparison, given several considerations. OEBs are completely health-based concentration ranges derived from the totality of the toxicity information available for a specific chemical substance. OELs, by contrast, are derived with additional considerations, including possible adjustments for analytical feasibility, engineering control achievability, and in some cases economic factors. Consequently, given these additional adjustments for OELs, the OEBs and OELs will not always align perfectly. Overall, however, the results of the evaluation exercises demonstrate that the occupational exposure banding process is accurate and reproducible and can be a useful tool for evaluating chemical substances that do not have OELs.

Although the occupational exposure banding process was developed for all chemical substances that lack OELs, it should not be applied to some, such as pharmaceutical drugs and radioisotopes. This document details other situations that warrant special consideration, such as banding nanomaterials or mixtures of two or more chemical substances.

A substantial number of chemical substances lack authoritative OELs, and risk management guidance is needed for these. Occupational exposure banding is one additional tool that can provide such guidance. An OEB provides a range of air concentrations that is expected to be protective of worker health. The process and adherence to the resultant OEB are voluntary and are not required or tied to any legal obligations. This document details the use and application of the occupational exposure banding process and provides a summary of efforts taken to evaluate its comparability to OELs and usability.

Occupational Exposure Banding at a Glance

Occupational exposure banding is a tool that can provide guidance for making risk management decisions when an authoritative OEL is not available. Occupational exposure bands not only provide a range of air concentrations expected to protect worker health but also can be used to identify potential health effects and target organs, identify health risks that necessitate health communication, inform implementation of control interventions and preparedness plans, inform medical surveillance decisions, and provide critical chemical toxicity information quickly.

Occupational exposure banding uses easily accessible qualitative and quantitative hazard information on selected health effect endpoints to identify potential inhalation-based exposure ranges or categories for guiding occupational risk assessment and risk management. The occupational exposure banding process provides a series of concrete steps to guide users through the evaluation of health hazard information and identification of the appropriate occupational exposure band from among five categories based on the severity of health outcomes (bands A to E; band A is highest air concentrations, and band E is lowest air concentrations) (Figure 0-1).

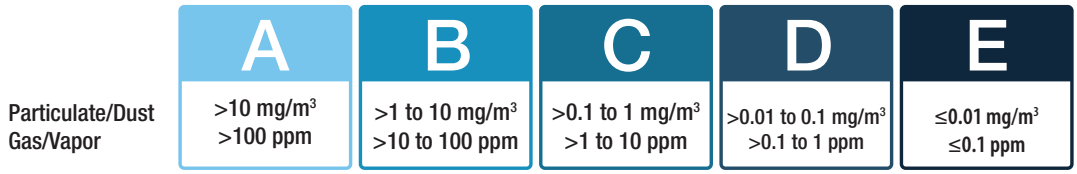


Figure 0-1. Occupational exposure bands [McKernan et al. 2016].

Note: When OSHA and other regulatory bodies limit occupational exposure to chemical substances, users should defer to those regulations, rather than an estimated occupational exposure band. For example, Particulates Not Otherwise Regulated (PNOR) have OSHA exposure limits of 15 mg/m^3 for total dust and 5 mg/m^3 for respirable fraction [29 CFR 1910.1000 Table Z-1] [OSHA 2012].

The banding process uses a three-tier approach (Figure 0-2). Selection of the most appropriate tier for a specific banding situation depends on the quantity and quality of the available data and the training and expertise of the user.

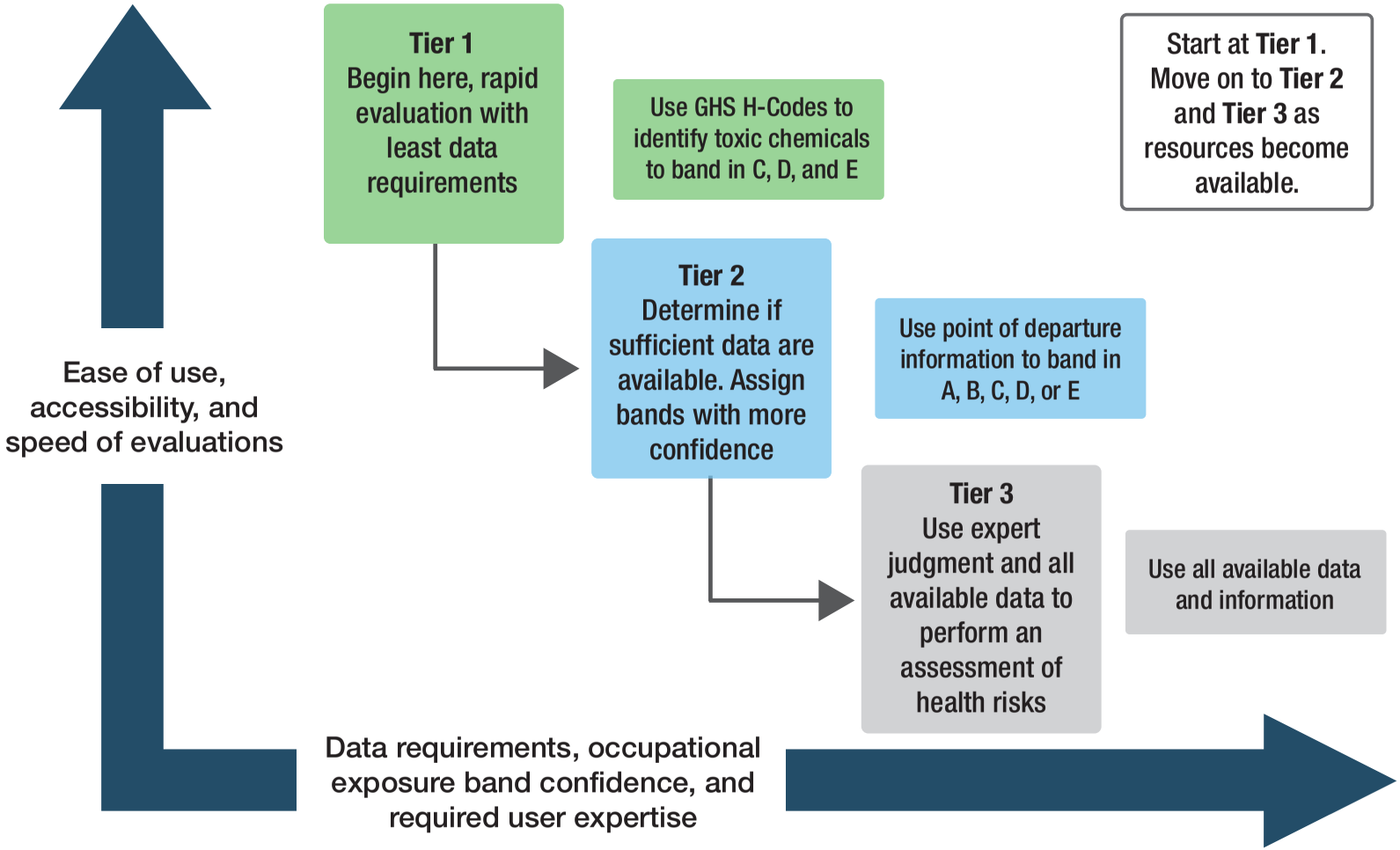
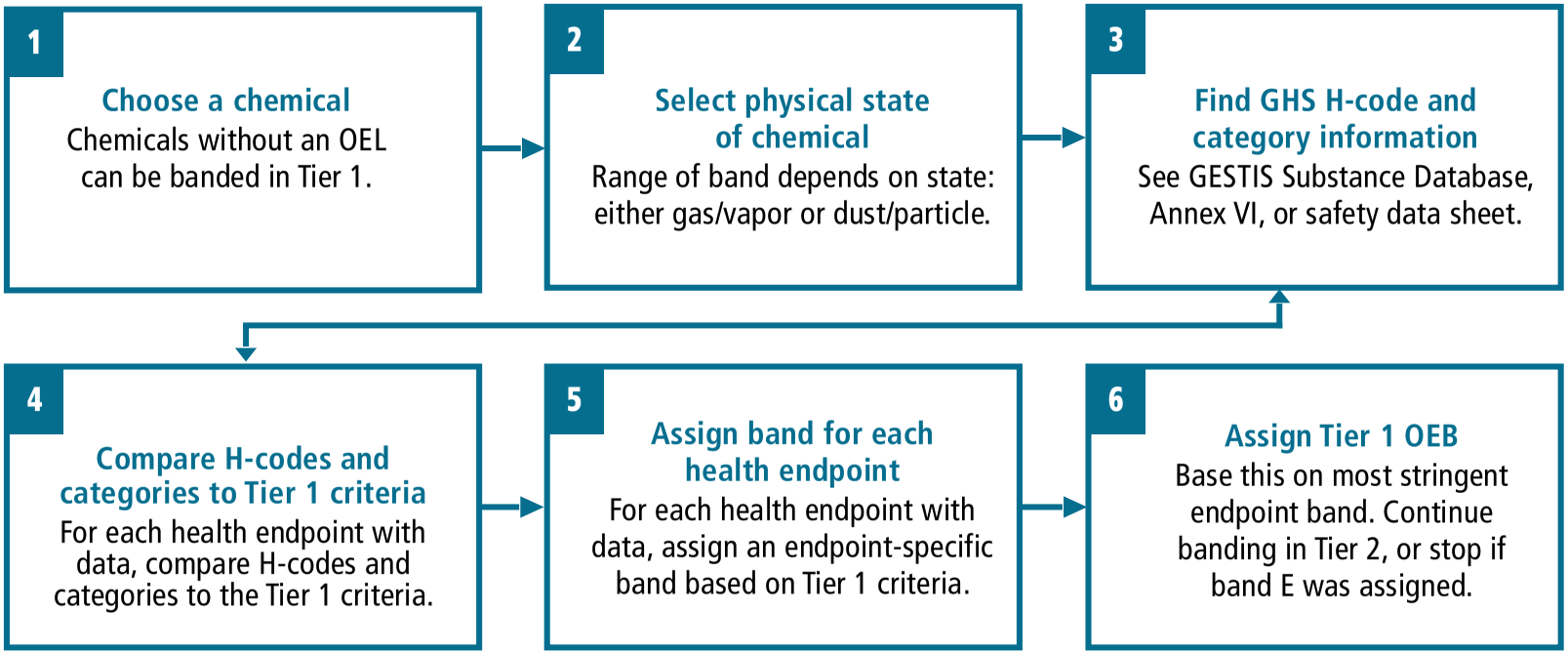


Figure 0-2. Three tiers in the occupational exposure banding process.

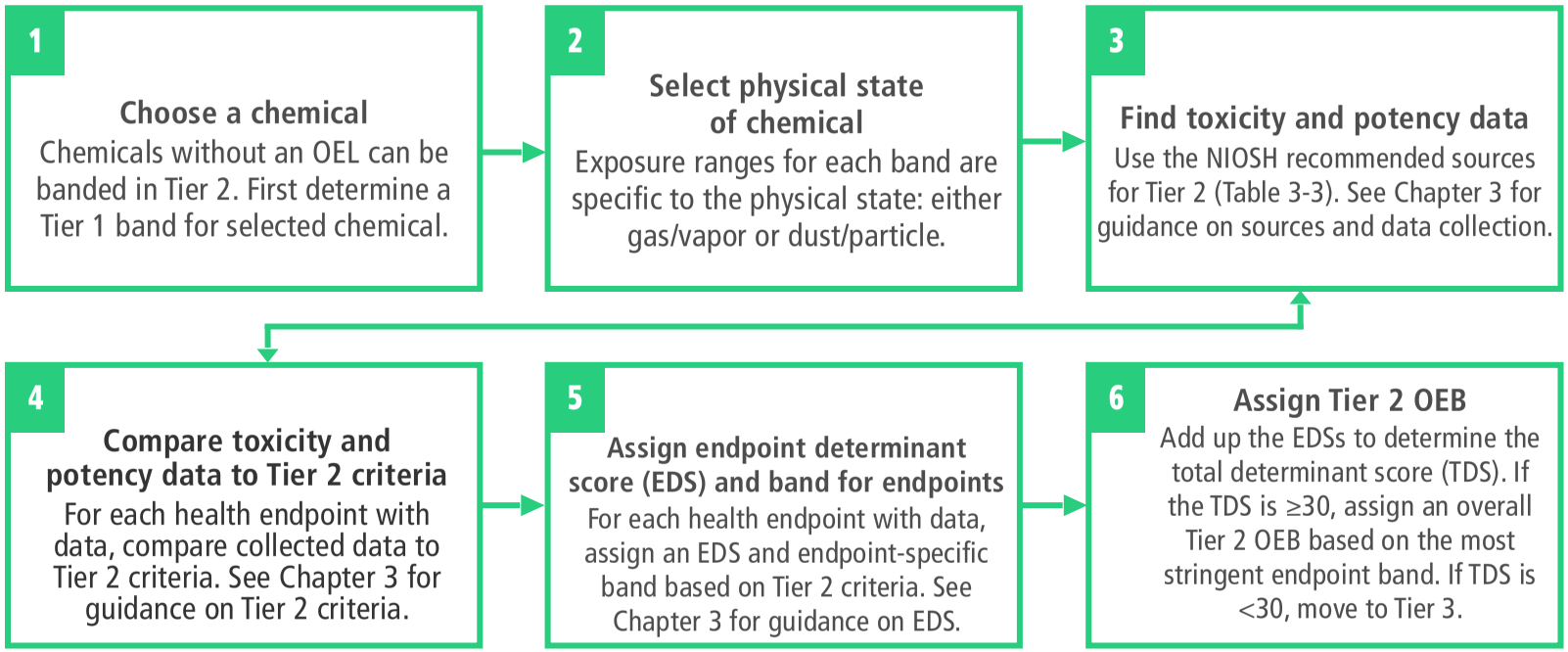
Tier 1 Overview

Tier 1 is a screening-level process based on the Globally Harmonized System of Classification and Labeling of Chemicals (GHS). In Tier 1, users assign OEBs on the basis of criteria aligned with specific GHS hazard codes (H-codes) and categories. Chemical substances with potential to cause serious or irreversible health effects at relatively low doses warrant assignments of band D or band E. Chemical substances that are likely to cause reversible health effects at higher concentrations are categorized in band C. Bands A and B are not assigned in Tier 1. Refer to Chapter 2 for more detailed information on Tier 1 and how to go through the Tier 1 process.



Tier 2 Overview

Tier 2 produces an OEB assignment based on data found in primarily authoritative sources. In Tier 2, users assign OEBs on the basis of key findings from prescribed literature sources. Intermediate knowledge of toxicology concepts is helpful. Some endpoints in Tier 2 are more quantitative than in Tier 1. Points of departure for some endpoints are selected according to the provided instructions. Chemical substances are assigned into bands A through E. Refer to Chapter 3 for more detailed information on Tier 2.



Tier 3 Overview

When a user wishes to analyze the potential human health effects of a chemical substance beyond Tier 2, or there are insufficient data to band a chemical in Tier 2, further evaluation may be required. This might involve a detailed survey of the relevant health effects literature and analysis of data on the nine health endpoints used in the Tier 1 and Tier 2 processes. Important elements of the Tier 3 process include (1) carrying out targeted literature searches of bibliographic databases and journal articles containing information on the chemical substance, (2) selecting critical studies of the chemical pertinent to each toxicological endpoint under consideration, (3) critically reading and evaluating the studies to discern the toxicological outcomes, including any available dose-response information, (4) using the scientific information to make decisions about the appropriate band for each health endpoint, and (5) determining the most stringent endpoint band and assigning that as the overall OEB.

For more detailed information and instructions on how to band a chemical substance with the occupational exposure banding process, refer to the occupational exposure banding e-Tool, accessible on the NIOSH website.

Occupational Exposure Banding e-Tool

The **NIOSH occupational exposure banding electronic tool (e-Tool)** is a supplementary online application that incorporates the occupational exposure banding process. It allows users to apply toxicology and potency information to generate an occupational exposure band for chemicals. The e-Tool provides users with an automated means to band chemical substances in Tier 1 and a simplified method for banding chemicals in Tier 2. Users can access the e-Tool at https://wwwn.cdc.gov/NIOSH-OEB/.

The Tier 1 process is fully automated. A Tier 1 band is generated automatically if the chemical of interest is found in the existing e-Tool database. For more information about the Tier 1 process, see the Tier 1 overview page. The Tier 2 process requires users to extract relevant data from recommended sources and can be time intensive, requiring up to several hours to effectively band chemical substances. For more information about the Tier 2 process, see the Tier 2 overview page for instructions and examples of how to band a chemical with the e-Tool.

Users must register with a business email and password to access the e-Tool and band chemicals. This requirement allows users to save their data or edit their entries at a later time. NIOSH will not use, sell, exchange, or otherwise release any account information, data, or chemical bands to anyone for any reason unless required by law.

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Contents

Abbreviations

ACGIH®	American Conference of Governmental Industrial Hygienists®
AIHA	American Industrial Hygiene Association
AOEC	Association of Occupational and Environmental Clinics
ATSDR	Agency for Toxic Substances and Disease Registry
BMCL	Benchmark concentration lower bound
BMDL	Benchmark dose lower bound
CalEPA	California Environmental Protection Agency
Cal OEHHA	California Office of Environmental Health Hazard Assessment
Cal/OSHA	California Occupational Safety and Health Administration
CAS	Chemical Abstracts Service
CFR	Code of Federal Regulations
EC3	Effective concentration that produces a stimulation index of 3 or more
EDS	Endpoint determinant score
ECHA	European Chemicals Agency
EU	European Union
GHS	Globally Harmonized System of Classification and Labelling of Chemicals
GLP	Good laboratory practices
GPMT	Guinea pig maximization test
H-code	Hazard code
HSE COSHH	Health and Safety Executive Control of Substances Hazardous to Health
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	Immediately dangerous to life or health
IRIS	U.S. EPA Integrated Risk Information System
IUR	Inhalation unit risk
Kg	Kilogram
LC_{50}	Median lethal concentration
LD_{50}	Median lethal dose
LLNA	Local lymph node assay
LOAEL	Lowest observed adverse effect level
MAK	Maximum workplace concentration (translated from German Maximale Arbeitsplatz-Konzentration)
mg/kg	Milligrams per kilogram
mg/m^3	Milligrams per cubic meter

MRL	Minimal risk level
MW	Molecular weight
NIOSH	National Institute for Occupational Safety and Health
NOAEL	No observed adverse effect level
NTP	U.S National Toxicology Program
OEB	Occupational exposure band
OECD	Organisation for Economic Cooperation and Development
OEL	Occupational exposure limit
OSHA	Occupational Safety and Health Administration
PEL	Permissible exposure limit
ppm	Parts per million
REACH	Registration, Evaluation, Authorization and Restriction of Chemicals (European Chemicals Agency)
RED	Reregistration Eligibility Decision document (EPA)
REL	Recommended exposure limit
RfC	Reference concentration
RfD	Reference dose
RoC	U.S. National Toxicology Program Report on Carcinogens
SCDM	Superfund Chemical Data Matrix (EPA)
SDS	Safety data sheet
SF	Slope factor
STOT	Specific target organ toxicity
STOT-RE	Specific target organ toxicity–repeated exposure
TC_{05}	Tumorigenic concentration for 5% of the population
TD_{05}	Tumorigenic dose for 5% of the population
TDC	Tolerable daily concentration
TDI	Tolerable daily intake
TDS	Total determinant score
TI	Tolerable intake
TiO_2	Titanium dioxide
TLV®	Threshold limit value®
TWA	Time-weighted average
US EPA	U.S. Environmental Protection Agency
WEEL	Workplace environmental exposure level®
WHO	World Health Organization
WOE	Weight of evidence

Glossary

Acute toxicity: adverse effects that occur following oral or dermal administration of a single dose of a substance, multiple doses given within 24 hours, or inhalation exposure of 4 hours

Aspiration toxicity: severe acute effects such as chemical pneumonia, varying degrees of pulmonary injury, or death following aspiration

Aspiration: the entry of a liquid or solid directly through the oral or nasal cavity, or indirectly from vomiting, into the trachea and lower respiratory system

CAS number: a unique numerical identifier assigned to chemical substances by the Chemical Abstracts Service (CAS)

Carcinogenicity: the ability of a chemical substance or a mixture of chemical substances to induce tumors, increase tumor incidence and/or malignancy, or shorten the time to tumor occurrence

Control banding: a strategy that groups workplace risks into control categories or bands on the basis of combinations of hazard and exposure information. The following four main control bands have been developed for exposure to chemical substances by inhalation.

Band 1: Use good industrial hygiene practice and general ventilation.

Band 2: Use local exhaust ventilation.

Band 3: Enclose the process.

Band 4: Seek expert advice.

This qualitative strategy to assess and manage risk focuses resources on exposure controls and describes how strictly a risk needs to be managed.

Corrosive to metals: a substance or a mixture that by chemical action will materially damage or even destroy metals

Endpoint: a marker of response from exposure to a physical, health, or environmental hazard

Endpoint determinant score: a specific score assigned to each endpoint, based on the presence or absence of endpoint-specific toxicological information

Explosive: a solid or liquid that is in itself capable by chemical reaction of producing gas at such a temperature and pressure and at such a speed as to cause damage to the surroundings

Eye irritation: changes in the eye, following the application of a test substance to the front surface of the eye, that are fully reversible within 21 days of application

Flammable aerosols: any gas compressed, liquefied, or dissolved under pressure within a non-refillable container made of metal, glass, or plastic, with or without a liquid, paste, or powder that is flammable

Flammable gas: a gas having a flammable range in air at 20°C and a standard pressure of 101.3 kilopascal (kPa)

Flammable liquid: a liquid having a flash point of not more than 93°C

Flammable solid: a solid that is readily combustible or may cause or contribute to fire through friction

Gases under pressure: gases that are contained in a receptacle at a pressure not less than 280 Pascal (Pa) at 20°C or as a refrigerated liquid

Germ cell mutagenicity: an agent that can cause permanent changes to the amount or structure of the genetic material in a germ cell (an ovum or sperm cell or one of their developmental precursors), thereby potentially resulting in the transfer of the mutation to the offspring of an exposed recipient, animal, or human

GESTIS substance database: a German Social Accident Insurance database that contains approximately 8,000 chemical substances with toxicological data; physical and chemical properties; regulations; and hazard statements, codes, and categories

Hazard category: the division of criteria within each hazard class (e.g., "oral acute toxicity" includes five hazard categories, and "flammable liquids" includes four hazard categories). These categories compare hazard severity within a hazard class and should not be taken as a comparison of hazard categories more generally.

Hazard class: the nature of the physical, health, or environmental hazard, e.g., flammable solid, carcinogen, oral acute toxicity

Hazard code: alphanumeric code used to designate a hazard statement

Hazard statement: a statement assigned to a hazard class and category that describes the nature of the hazards of a chemical substance or chemical mixture, including, where appropriate, the degree of hazard

Mixture: a solution comprising two or more substances that do not react

Mutagen: an agent giving rise to an increased occurrence of mutations in populations of cells and/or organisms

Occupational exposure banding: also called hazard banding; a systematic process that uses qualitative or quantitative hazard information on selected health-effect endpoints to identify potential inhalation-based exposure ranges or categories for guiding occupational risk assessment and risk management

Occupational exposure band: the range of air-concentration levels expected to be protective of worker health. The bands range from A (highest range of exposure concentrations) to E (lowest range).

Occupational exposure banding e-Tool: a supplementary online application that incorporates the occupational exposure banding process by allowing users to apply toxicology and potency information to generate quantitative exposure guidance for chemical substances

Occupational exposure limit: an upper limit on the acceptable concentration of hazardous substance in workplace air for a particular material or class of materials. OELs may apply to ceiling, short-term exposure limits (STELs), or time-weighted average (TWA) limits.

Organic peroxide: an organic liquid or solid that contains the bivalent -0-0- structure and may be considered a derivative of hydrogen peroxide, where one or both of the hydrogen atoms have been replaced by organic radicals

Oxidizing gas: any gas that may, usually by providing oxygen, cause or contribute to the combustion of other material more than air does

Oxidizing liquid: a liquid that in itself is not necessarily combustible but may, generally by yielding oxygen, cause or contribute to the combustion of other material

Oxidizing solid: a solid that in itself is not necessarily combustible but may, generally by yielding oxygen, cause or contribute to the combustion of other material

Pyrophoric liquid: a liquid that, even in small quantities, is liable to ignite within 5 minutes of coming into contact with air

Pyrophoric solid: a solid that, even in small quantities, is liable to ignite within 5 minutes of coming into contact with air

Reproductive toxicity: the ability of a substance to induce adverse effects on sexual function or fertility in adult males or females or adverse developmental effects in offspring

Respiratory sensitizer: a substance that induces hypersensitivity of the airways following its inhalation

Self-heating substance: a solid or liquid, other than a pyrophoric substance, which is liable to self-heat by reaction with air and without energy supply. This endpoint differs from a pyrophoric substance in that it will ignite only when in large amounts (kilograms) and after long periods of time (hours or days).

Self-reactive substance: a thermally unstable liquid or solid liable to undergo a strongly exothermic thermal decomposition even without participation of oxygen (air)

Serious eye damage: the production of tissue damage in the eye or serious physical decay of vision, following application of a test substance to the front surface of the eye that is not fully reversible within 21 days of application

Skin corrosion: the production of irreversible damage to the skin following the application of a test substance for up to 4 hours

Skin irritation: the production of reversible damage (excluding allergic responses) to the skin following the application of a test substance for up to 4 hours

Skin sensitizer: a substance that may induce an allergic response following skin contact

Specific target organ toxicity–repeated exposure: all significant health effects, not otherwise specifically included in the Globally Harmonized System of Classification and Labeling of Chemicals, that can impair function after repeated exposure to a substance. The effects can be reversible, irreversible, immediate, and/or delayed.

Specific target organ toxicity–single exposure: all significant health effects, not otherwise specifically included in the Globally Harmonized System of Classification and Labeling of Chemicals, that can impair function after a single exposure to a substance. The effects can be reversible, irreversible, immediate, and/or delayed.

Substance, or chemical substance: any material that has definite chemical composition. Moreover, a pure substance cannot be separated into other substances by any mechanical process. Chemical elements and compounds are substances, mixtures are not.

Total determinant score: a quantitative measure of data sufficiency of a compound for banding in Tier 2 of the evaluation. Total determinant score comprises the sum of endpoint determinant scores assigned for the availability of endpoint-specific toxicological information. A threshold of 30 out of a maximum possible score of 125 marks a chemical-specific data set as sufficient for banding in Tier 2.

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Chapter 1

Introduction to Occupational Exposure Banding

1.0 Occupational Exposure Banding: Definition

Occupational exposure limits (OELs) have been an important component of the practice of occupational hygiene for decades [Schulte et al. 2010; Nikfar and Malekirad 2014; Skowroń and Czerczak 2015; Deveau et al. 2015; Cook 1987; Paustenbach 1998]. Occupational hygienists develop and implement control strategies largely based on the relevant OELs that are available to them. Exposures to chemical substances at concentrations above their OEL may cause harm, and hygienists act to ensure that workers are not exposed to concentrations of hazardous chemical substances that exceed their designated OELs. Unfortunately, the rate that chemical substances have been introduced into commerce has significantly outpaced the development of authoritative (i.e., governmental, consensus, or peer reviewed) OELs [OSHA 2014]. The U.S. Environmental Protection Agency (EPA) reports that the Toxic Substances Control Act Chemical Substance Inventory contains over 85,000 chemical substances [EPA 2015], yet only about 1,000 chemical substances have been assigned at least one authoritative OEL (see Figure 1-1).

As NIOSH and other government, international, and professional agencies continue to develop new OELs and update current OELs, guidance is needed for the thousands of chemical substances workers are exposed to that lack reliable exposure limits. The occupational exposure banding process uses chemical toxicity data to assign a range of concentrations to which chemical exposures should be controlled. The output of the occupational exposure banding process is an occupational exposure band (OEB) that defines the range of air concentrations expected to be

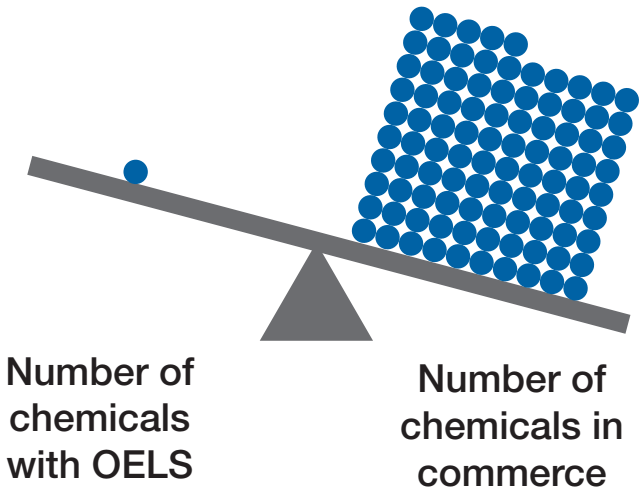

Figure 1-1. Chemical substances in commerce vs. chemical substances with occupational exposure limits.

protective of worker health. Thus, occupational exposure banding is one of a number of strategies used to address worker and emergency responder safety and health when the time, data, and resources needed for OEL development are not available. The NIOSH occupational exposure banding process is a resource (among others) to provide recommendations for limiting chemical exposures in the workplace, based on a chemical substance's toxicity. Using the occupational exposure banding process to band chemical substances for which authoritative OELs are available is not recommended. Furthermore, the process and adherence to the resultant OEB are voluntary and are not required or tied to any legal obligations. The intent of the NIOSH occupational exposure banding strategy is to provide a means to assess many of the chemical substances for which guidance is lacking, thereby providing another means for informing chemical risk management decisions.

Sometimes referred to as hazard banding or health hazard banding, occupational exposure banding is defined as a systematic process that uses qualitative or quantitative hazard information on selected health effect endpoints to identify potential inhalation-based exposure concentration ranges or categories for guiding occupational risk assessment and risk management. In the context of this document, the term exposure refers to human contact with a chemical substance in the work environment. For chemical substances, exposure usually occurs through inhalation, ingestion, or contact with the skin, eye, mucous membranes, or other parts of the body. The term hazard is used herein to describe potential threats to life, health, or well-being. Hazardous chemical substances have the potential to cause harm to individuals who are exposed to them. The purpose of occupational exposure banding is to reduce the risk to workers who are exposed to chemical substances in the workplace. Risk is defined as the probability that a person will experience adverse effects after exposure to hazardous chemical substances. Occupational exposure banding can be an effective tool to assess and manage risk to workers.

The concept of using hazard-based categories to communicate potential health concerns, alert employers and workers to the need for risk management, and inform exposure control requirements is not new. Numerous hazard classification and category-based systems have seen extensive use in the occupational setting [Egeghy et al. 2011; Zalk and Nelson 2008; Shin et al. 2014; Scheffers et al. 2016]. Such systems are deeply embedded in occupational hygiene practice, particularly in the pharmaceutical industry [Naumann et al. 1996], and are also elements of well-developed, modern hazard communication programs (e.g., UN 2013 Globally Harmonized System of Classification and Labelling of Chemicals).

As previously mentioned, most guidance on hazardous chemical substances has been in the form of OELs rather than OEBs. The science and art of evaluating hazardous chemical substances in the workplace and determining levels of exposure (i.e., OELs) that are associated with minimal risk of adverse health effects have a mature history in the promotion of occupational safety and health [Binks 2003; Laszcz-Davis et al. 2014; Maier et al. 2015]. Despite this history, derivation of OELs remains a resource-intensive process that requires exposure data, epidemiologic and/or toxicological data, risk assessment methodology, and other considerations [Schulte et al. 2010; Paustenbach and Langner 1986]. For example, authoritative OELs such as the Occupational Safety and Health Administration (OSHA) permissible exposure limits (PELs) require that a quantitative risk assessment and other elements such as analytical feasibility, technological achievability, and economic feasibility be considered. Consequently, the proportion of chemical substances in use for which government, consensus, or peer-reviewed OELs have been published in the last half-century of practice is relatively low: roughly 2,000 OELs covering approximately 1,000 chemical substances. In many cases, multiple organizations have assigned different OELs

to the same chemical substances. At the same time, the U.S. EPA has estimated that 85,000 hazardous chemical substances are commercially available in the United States [EPA 2015], and according to OSHA over 40 million employees are now potentially exposed to hazardous chemical substances in over 5 million workplaces [OSHA 2012]. The characterization of the potential adverse health effects of chemical and physical substances is one of the foundations of occupational hygiene as a public health practice [OSHA 1998]. Therefore, strategies for expedited assessment and characterization of hazardous chemical substances are needed to inform occupational risk management decisions and protect worker health.

The NIOSH occupational exposure banding process guides a user through the evaluation and selection of critical health hazard information to identify the appropriate OEB from among five categories of exposure ranges based on the potency of the chemical substance (bands A to E; band A is least severe and band E is most severe). Thus, the OEBs reflect toxicity potency ranges, where band A chemical substances have the lowest health hazard potential (and thus higher exposure ranges), and band E chemical substances have the highest health hazard potential (Figure 1-2) [McKernan et al. 2016].

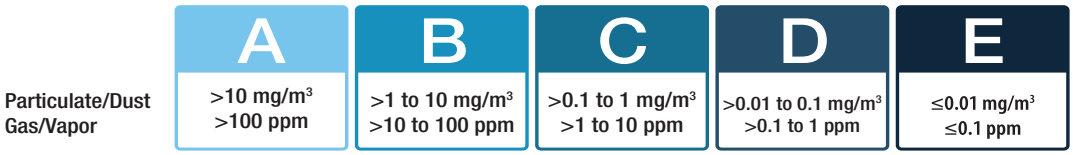

Figure 1-2. Occupational exposure bands [McKernan et al. 2016].

Note: When OSHA and other regulatory bodies limit occupational exposure to chemical substances, users should defer to those regulations rather than an estimated occupational exposure band. For example, particulates not otherwise regulated (PNOR) have OSHA exposure limits of 15 mg/m^3 for total dust and 5 mg/m^3 for respirable fraction [29 CFR 1910.1000 Table Z-1][OSHA 2012].

Occupational exposure banding aligns with the professional practice framework of anticipation, recognition, evaluation, control, and confirmation of protection from health hazards [Laszcz-Davis et al. 2014; Jahn et al. 2015]. Furthermore, occupational exposure banding will assist in the qualitative aspects of risk management by providing relative hazard bands for chemical substances being reviewed [OSHA 1998]. Through a consistent and documented process for characterizing hazardous chemical substances according to recommended OEBs, timely and informed risk management decisions can be made for chemical substances lacking OELs. This process can also be used to prioritize chemical substances for which OELs should be established [McKernan and Seaton 2014]. In addition, the occupational exposure banding process can be used to identify additional data needs to establish OELs. Finally, occupational exposure banding packages information in a way that facilitates hazard communication and provides critical information quickly. Following the banding process allows the user to identify health risks that inform health communication, implementation of control interventions, and medical surveillance decisions. It should be noted that occupational exposure banding does not consider technical or economic feasibility of controlling exposure to the range recommended by the banding process or the feasibility of reliably measuring exposure at that level. Rather, NIOSH sought to develop and evaluate the occupational exposure banding process and supporting guidance for use in assessing

and characterizing hazardous chemical substances in the workplace. This document outlines the NIOSH process as the result of that effort.

Although the NIOSH occupational exposure banding process provides exposure ranges for each band that can serve as a guide for risk management, the occupational exposure banding process is distinct from the concept of control banding. For OEBs, the process uses only hazard-based data (e.g., studies on human health effects or toxicology studies) to identify an overall level of hazard potential and associated airborne concentration range for chemical substances with similar hazard profiles. While occupational hygienists can use the output of this process to make risk management and exposure control decisions, the process does not supply such recommendations directly. In contrast, control banding methods, such as the United Kingdom Health and Safety Executive Control of Substances Hazardous to Health (HSE COSHH) essentials, link hazards to specific control measures [HSE 2013; Zalk et al. 2010; Zalk and Nelson 2008; Beaucham et al. 2012; NIOSH 2009c; AIHA 2007] (see also http://www.hse.gov.uk/coshh/basics.htm). For this reason, although the occupational exposure banding process can ultimately inform risk management and control decisions, in itself it is not control banding, as demonstrated in Figure 1-3.

The control banding approach has utility in the field but has some limitations. The HSE COSHH essentials, for example, provide one of four very general control recommendations (use general ventilation, use local exhaust ventilation, enclose the process, or seek expert advice) based on simplistic inputs from the user. The occupational exposure banding process was developed to ensure a rigorous scientific foundation that has been evaluated to ensure confidence in the OEB assignments. The development of OEBs requires more sophisticated inputs and thus yields a more refined output. Additionally, the purpose of OEBs is not to directly link to a control strategy but rather to define a range of air concentrations to protect worker health. The information provided by OEBs, in concert with exposure assessment, can be used to evaluate the effectiveness of the controls that are in place and help to determine whether additional controls should be implemented.

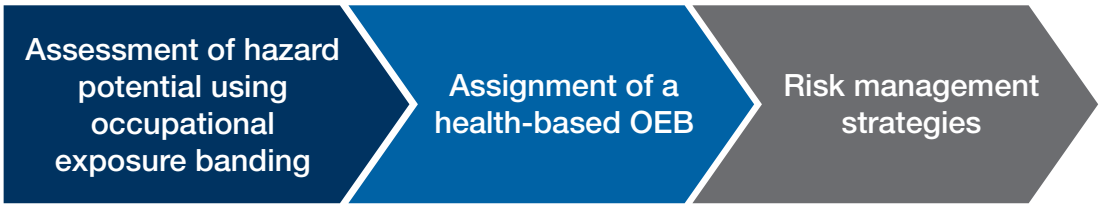

Figure 1-3. Potential use of occupational exposure banding for the development of risk management strategies.

1.1 History of Occupational Exposure Banding Applications

Companies with significant in-house occupational hygiene, toxicology, chemistry, and occupational medicine expertise have used the hazard banding approach for decades to establish exposure control limits or ranges for chemical substances for which no full OEL has been developed [Naumann et al. 1996; Paustenbach and Langner 1986]. Although use of hazard banding techniques was already well established at the time, an early journal publication on the approach highlighted application of "performance-based exposure control limits" in the pharmaceutical sector [Naumann et al. 1996; Sargent and David 1988].

The hazard banding technique remains well accepted among the pharmaceutical and larger chemical-processing risk assessment communities [Farris 2006; Naumann et al. 1996; Sargent and David 1988]. The continued interest in OEBs and hazard-based exposure control limits indicates a desire within the health and safety community to assess and share information about hazardous chemical substances. The need for this effort is supported by the observation that most chemical substances in commerce—and thus encountered in workplaces—have no published occupational exposure guidelines. This paucity of chemical-specific guidance, coupled with a new accessible process, provides an immediate and opportune environment for developing additional risk assessments. In addition to the OEBs providing interim risk management guidance for chemical substances without OELs, the occupational exposure banding process can be used to (1) array the available hazard data and identify key data gaps, (2) prioritize chemical substances for full OEL development, based on data availability and overall hazard profile, and (3) conduct a quality assurance review for overall consistency in OEL derivation.

The need for increased use of occupational exposure banding has been discussed in the occupational hygiene community [Ripple 2009] and has also been adopted by the volunteer Workplace Environmental Exposure Limits (WEEL®) Committee [Maier 2009]. The occupational exposure banding concept has also gained acceptance as part of a continuum of exposure guide values for occupational risk assessment, a concept being formalized in the occupational hygiene community as part of the hierarchy of occupational exposure guidance strategies [Laszcz-Davis et al. 2014; McKernan and Seaton 2014; Deveau et al. 2015; Jahn et al. 2015] (see Figure 1-4). In this hierarchy, OELs and other exposure guidance values are categorized on the basis of how much toxicological and epidemiological data are required to develop each limit. Quantitative,

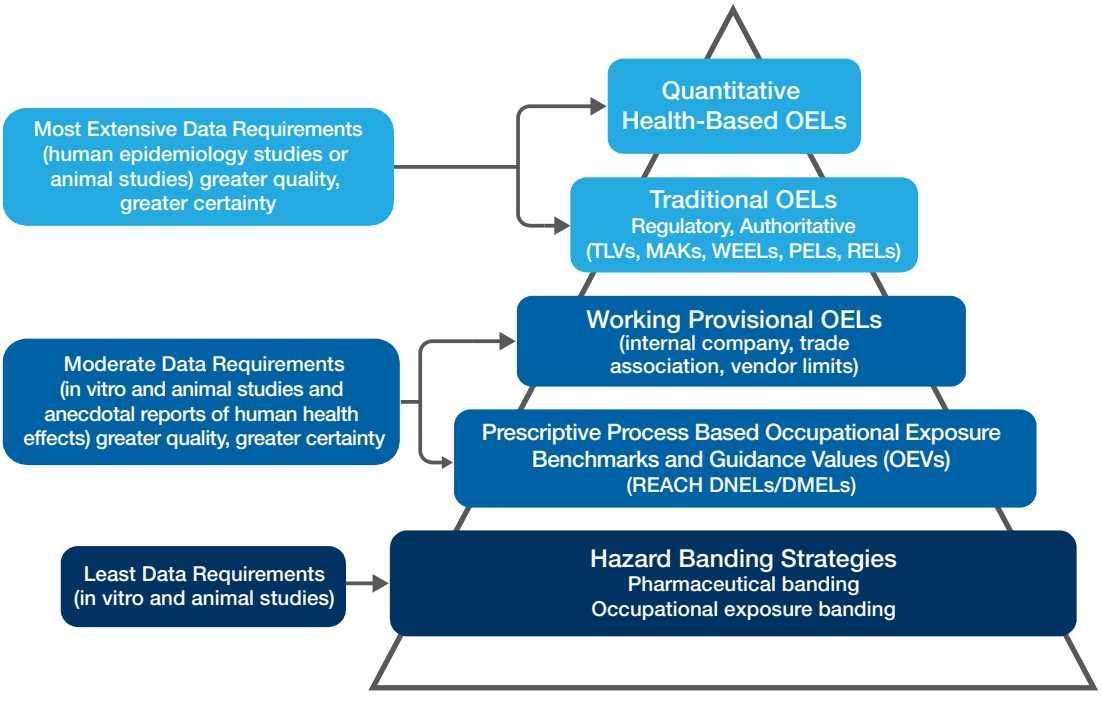

Figure 1-4. Hierarchy of exposure control guidance values [adapted from Laszcz-Davis et al. 2014; Jahn et al. 2015].

health-based OELs are at the top of the hierarchy. These OELs have the most extensive data requirements and are often considered the most precise. The amount and quality of data needed to form quantitative, health-based OELs are not always available for every potentially hazardous chemical substance, so alternate strategies must be employed to develop health-protective limit values.

These alternative methods are found further down the hierarchy as the data requirements are reduced. It is important to note that traditional OELs often vary in the quantity and quality of data supporting their development, based on when they were assigned and the process used to develop them. Health hazard banding strategies are at the lowest level of the hierarchy, including the NIOSH process for occupational exposure banding. Because the data requirements to determine an OEB are much lower, the precision of the band is also reduced; therefore, by design, occupational exposure banding strategies tend to result in lower concentration ranges than other processes for developing OELs, in order to ensure the bands are more health-protective [Laszcz-Davis et al. 2014; Deveau et al. 2015].

1.2 Features of the NIOSH Occupational Exposure Bands

The NIOSH occupational exposure banding process shares similar scientific underpinnings with the exposure banding processes many organizations use [Naumann et al. 1996]. Key aspects of the process shared by most organizations include the following:

- Collecting the data to facilitate evaluation of individual health effect endpoints
- Comparing the hazard data for each endpoint to criteria (qualitative or quantitative) for that endpoint
- Identifying the endpoints that appear to generate the greatest level of hazard, leading to selection of an overall hazard band
- Assigning the band and associated inhalation exposure concentration range.

To date, few published processes or resources facilitate harmonization of different occupational exposure banding approaches among the occupational hygiene community. NIOSH seeks to address this deficit by providing a comprehensive exposure banding process with broad application and utility.

Some key features of the NIOSH occupational exposure banding process distinguish it from other common hazard classification and category-based systems. One key feature is the use of the OEB as a tool for considering the overall hazard profile for multiple health hazard endpoints at the same time. The band-specific technical criteria apply to nine potential toxicological or human health outcomes: (1) carcinogenicity, (2) reproductive toxicity, (3) specific target organ toxicity, (4) genotoxicity, (5) respiratory sensitization, (6) skin sensitization, (7) acute toxicity, (8) skin corrosion and irritation, and (9) eye damage/irritation. The integration of each of the hazards yields the identification of an OEB that considers the severity of hazard posed for numerous health endpoints relevant to worker health. The overall band is assigned on the basis of protection against the most severe effects.

This process goes beyond hazard classification systems such as GHS that identify each relevant hazard independently without providing an overall assessment to guide risk assessment and management. However, NIOSH occupational exposure banding endpoints are aligned with GHS, and the process relates potency of each occupational exposure banding endpoint to GHS hazard

statements and categories, when possible. The NIOSH occupational exposure banding process also is more comprehensive than systems such as the hazardous materials information system process, which gives a single integrated hazard category based on limited, usually acute toxicity or lethality endpoints. The OEB has improved utility for hazard communication compared to these other systems because it highlights the endpoints that are most likely to affect overall worker risk.

A second key feature of the NIOSH occupational exposure banding process is the linkage of hazard-based categories (i.e., bands) to airborne concentration ranges. The corresponding exposure concentration ranges for each of the five NIOSH OEBs are designated by the letters A through E and are listed in Table 1-1. Airborne concentration ranges associated with occupational exposure bands. This process improves the utility of the hazard-based system by providing a target airborne concentration range that can be used for traditional occupational risk management purposes such as assessing the adequacy of exposure control strategies. These exposure ranges are intended to reflect the range of full-shift OELs that would be expected for a chemical substance with a similar hazard profile. Because OEBs are often based on smaller health effect data sets or less detailed analyses than those of traditional OELs, they should be used with this limitation in mind for supporting risk management decisions.

Table 1-1. Airborne concentration ranges associated with occupational exposure bands.

Occupational exposure band	Airborne target range for dust or particle concentration (milligrams per cubic meter of air [mg/m^3])	Airborne target range for gas or vapor concentration (parts per million [ppm])
A	>10	>100
B	>1 to 10	>10 to 100
C	>0.1 to 1	>1 to 10
D	>0.01 to 0.1	>0.1 to 1
E	≤0.01	≤0.1

As currently practiced, hazard banding requires a significant amount of technical expertise in occupational hygiene, which limits the size of the immediate user community. To address this limitation, the NIOSH process uniquely provides a three-tiered assessment process that allows for the application of the technique with traditional occupational hygiene expertise, along with the option of more in-depth processes in consultation with specialists in occupational medicine and toxicology (see Figure 1-5). The three tiers in the process include:

- **TIER 1:** Qualitative: OEB assignment based on GHS. Tier 1 involves assigning the OEB on the basis of criteria aligned with specific GHS H-codes and categories. It is intended for individuals with basic toxicology knowledge. Chemical substances with potential for irreversible health effects at relatively low doses warrant assigning band D or band E. Chemical substances that are likely to cause reversible health effects are categorized in band C. Bands A and B are not assigned in Tier 1. Because Tier 1 has relatively low data requirements, there is not enough information or confidence in the GHS H-codes and categories to suggest exposure ranges for bands A and B in Tier 1. In general, Tier 1 can be used as a quick screening method, and NIOSH recommends going to Tier 2 if user expertise and data are available.

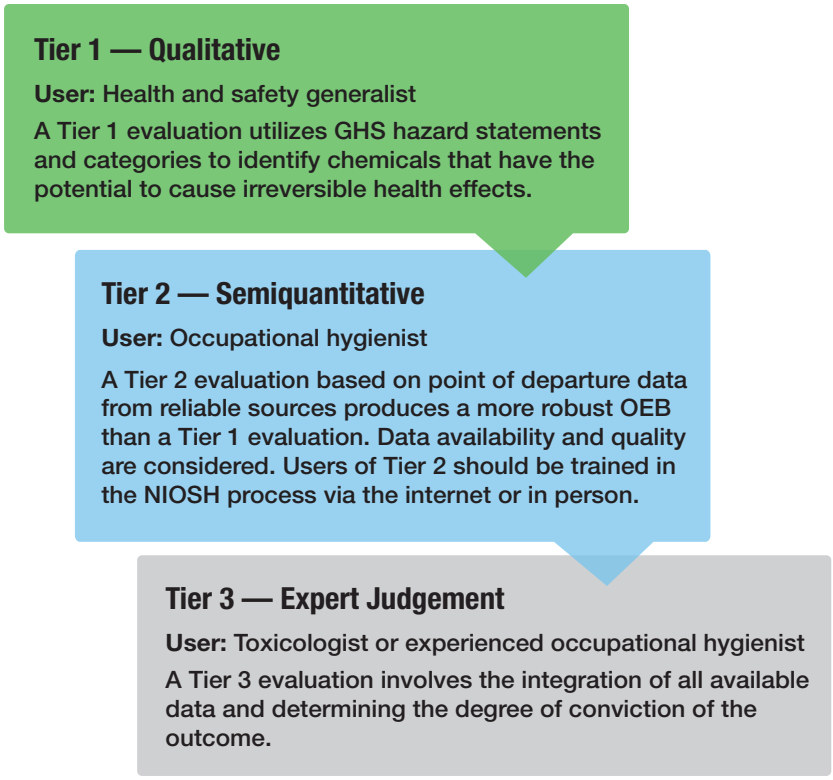

Figure 1-5. The three tiers of the NIOSH occupational exposure banding process.

- **TIER 2:** Semi-quantitative: OEB assignment based on secondary sources. Tier 2 involves assigning the OEB on the basis of key findings from prescribed literature sources, including use of data from specific types of studies. It is intended for individuals with intermediate toxicology knowledge. Tier 2 is more quantitative in nature than Tier 1. Individuals performing Tier 2 assessments will need to determine a point of departure by using the instructions that are provided for endpoints to support assigning chemical substances into bands A, B, C, D, or E. NIOSH recommends that users band a chemical substance in Tier 2 in all cases where there are enough data to conduct Tier 2 banding.
- **TIER 3:** Expert judgement: OEB based on primary sources and expert judgement. Tier 3 involves the use of expert judgement to assign the OEB on the basis of in-depth review of health effects studies. It should be performed only by individuals with advanced toxicology knowledge. Tier 3 involves a more quantitative, comprehensive evaluation of the scientific information and requires integration of all available data to determine the band assignment.

A third key feature of the NIOSH process is the incorporation of technical features that address challenges in traditional applications of the occupational exposure banding process. One such feature is the inclusion of a process for systematic decision-making to determine if the available data for a chemical substance are adequate to assign a band with reasonable confidence. The approach used in the occupational exposure banding process is to include the calculation of a total determinant score (TDS) for the chemical substance being evaluated. The TDS is a measure of the availability of qualitative and quantitative data across all endpoints. The presence or absence

of data for each health endpoint results in an endpoint determinant score (EDS), and the TDS is the sum of the EDS values. The TDS is a weighted score that considers both the endpoints for which data are available and the overall relevance or impact to the assessment of risk. For example, the occupational exposure banding process provides for a systematic documentation of data availability and whether data are available for a sufficient array of separate endpoints to assign an OEB. This process has the following key uses:

- Documents the data availability for each of the nine potential toxicological endpoints and/or health outcomes. This process can guide new data development priorities.
- Documents whether data are sufficient to assign a band. If not, the hierarchy of OEL concept can be used, and alternative techniques such as the threshold of toxicological concern [Dolan et al. 2005] might be used.

1.3 Evaluation of the Process

Occupational exposure banding, like other hazard or dose-response tools for occupational risk assessment, is one of many processes that occupational hygienists use for evaluation of workplace hazards. The occupational exposure banding process has been developed so that it closely aligns with anticipated OELs for chemical substances with similar hazard profiles, while erring on the side of health protection. In this document, an OEB is described as being at least as health-protective as, or more health-protective than, the lowest OEL when the concentration range of the OEB includes the OEL or is more stringent than the OEL. Typically, lower exposures are thought to be more protective of worker health.

To calibrate the occupational exposure banding process, the alignment between the OEBs and current OELs was evaluated. In a previous study, researchers [Brooke 1998] evaluated the effectiveness of a new UK scheme that uses toxicological hazard information to assign chemical substances to hazard bands. The UK scheme used risk phrases (R-phrases), which were assigned under the European Union (EU) classification scheme, to assign chemical substances to one of five toxicological hazard bands (A–E). Like the NIOSH process, each band represents a different target airborne-exposure range for dust/particles and gases/vapors. In the UK study, 111 chemical substances were banded by using the UK scheme, and the target airborne-exposure concentration range associated with the hazard band for a specific chemical substance was compared with the numerical value of the OEL. Results of this study showed that for 98% of the chemical substances, the target exposure for hazard banding was more stringent than the OEL [Brooke 1998].

In this current effort, NIOSH compared the Tier 1 and Tier 2 banding results for 606 chemical substances with available OELs from selected authoritative sources. More specifically, OEBs were compared to the lowest available concentration values among several governmental, consensus, and peer-reviewed OELs. A detailed description of the evaluation results is available in Chapter 6. Overall, the derived bands were at least as stringent as the OEL for 91.5% of the Tier 1 and 98% of the Tier 2 comparisons of combined gas/vapor and dust/particle chemical substances. Comparing OEBs with OELs is a rough estimate, since OEBs and OELs are different types of exposure limits. OEBs are health (toxicity) based, whereas OELs also include analytical feasibility and economic considerations that generally drive them lower than OEBs. Overall, the analyses demonstrate that the NIOSH occupational exposure banding process is consistent with OELs and reproducible.

1.4 OEB—Considerations for Application of the Range of Concentrations

The occupational exposure banding process uses endpoint-specific criteria to assign an OEB based on available toxicity information. Each band corresponds to a range of airborne concentrations to assist with risk management decisions.

The inhalation exposure concentration ranges associated with an OEB contrast with a traditional OEL, which is typically a single value. Despite the differences in how OEBs and OELs are derived, the interpretation and use of the OEB and its associated concentration range are similar to the traditional occupational hygiene practice for OELs. Despite being single airborne concentrations, OELs are not precise estimates of a cut-point between no adverse effect and adverse effect. Most OELs are derived by weighing the relevant data in a process that includes selection of a measure of toxic potency (the point of departure) and application of uncertainty factors. OEBs were designed to be used as an 8-hour time-weighted average (TWA) exposure range similar to OELs. However, users should be aware that chemical substances can have short-term health effects as well. The occupational exposure banding process is not designed to develop short-term exposure limits. The uncertainty in an OEL depends on the level of confidence in the underlying data and the extrapolation involved. An OEB is intended to provide a credible range for risk management rather than a single point.

Many organizations apply the concept of hazard-based banding strategies, such as the NIOSH occupational exposure banding process, as a supportive component of a risk management strategy. Occupational exposure banding and related categorical hazard assessment processes are key components of current control banding techniques. The value of a banding strategy is that it does not attempt to force inappropriate precision from the hazard analysis. A categorical view of the bands also aligns with the practical consideration that exposure control strategies are also categorical in nature. In practice, combinations of controls available for a given exposure scenario are not infinite. The use of the bands as control ranges is consistent with common applications of the control banding procedure. With such an approach, an organization implementing the occupational exposure banding process might have a default suite of control requirements for each band. Thus, a band A chemical substance might require only standard workplace precautions, whereas a band E chemical substance might require use or handling only with full containment methods. Each control regime would have been vetted for ability to control to the lowest concentration in the band. In that case the lower end of the band is often used as the default for exposure control. The use of the lower end of the band is the most health-protective strategy if additional chemical-specific assessments are not being made to refine the OEB or the resulting default control strategies.

An advantage of occupational exposure banding over other categorical approaches is that it allows for further customization of risk management procedures by providing an exposure range within the OEB. Some stakeholders may select an exposure range of 10% of the OEB, whereas others may select an exposure range that includes the median or 75% of the OEB. The decision of which exposure range should be used is based on the individual scenario involved. Selection of any point estimate within the range would typically reflect a deeper level of evaluation of the data that provides more specificity than the Tier 2 process.

Chapter 2

The Tier 1 Occupational Exposure Banding Process—Using GHS Information

2.0 Tier 1 Overview

The Tier 1 technical criteria use hazard phrases, codes, and categories of GHS, which cover most hazardous chemical substances and provide a uniform approach for communicating hazards related to chemical exposures. Under GHS, chemical substances are assigned standardized H-codes and categories based on their known toxicological characteristics [UNECE 2015]. As shown in Table 2-1, Tier 1 relies on the use of this information to assign OEBs. **Bands A and B are not assigned in Tier 1**. Because the data requirements for Tier 1 are relatively low, there is not enough information or confidence in the GHS H-codes and categories to suggest the higher exposure ranges of bands A and B for chemical substances banded in Tier 1. This cautious approach decreases the likelihood of allowing overexposures based on the limited data being used to develop a Tier 1 band. In order to get a more precise band, users should always proceed to Tier 2. The GHS H-codes and categories assigned to a chemical substance of interest can be found on an OSHA-compliant safety data sheet (SDS), as well as in a number of databases that address chemical safety. Detailed information on GHS H-codes and categories is available in Section 2.1.

GHS H-codes and categories provide a basis to categorize chemical substances according to the severity and reversibility of the health effects. Chemical substances that have the potential to cause severe and irreversible health effects at relatively low doses, such as carcinogens, reproductive toxicants, acutely fatal compounds, and corrosive materials, are systematically assigned to the most stringent bands. Chemical substances that cause reversible health effects at higher doses, such as skin and eye irritants, are assigned less stringent bands, given that the health outcomes are less severe. As shown in the Tier 1 overview (Figure 2-1), GHS H-codes and categories are used to discriminate between extremely potent chemical substances (assigned to bands D or E) and those for which the data suggest a lower level of toxicity. If a chemical substance has not been evaluated in the GHS system, it cannot be banded in Tier 1. Additionally, chemical substances that have been evaluated by GHS but have not been assigned any 300-level H-codes cannot be banded in Tier 1. These chemical substances require a Tier 2 evaluation for band assignment. In general, Tier 1 is intended to be used as a quick screening method, and NIOSH recommends using Tier 2 if the user expertise and requisite toxicology or other health data are available. Tier 1 would likely be most useful when banding a large number of chemical substances and deciding which ones should be prioritized for elimination, substitution, or further evaluation.

Table 2-1. Tier 1 criteria overview: GHS H-codes and categories for Tier 1*.

NIOSH Tier 1 Criteria	C	D	E
Exposure ranges			
Dust/particle	>0.1 to ≤1 mg/m^3	>0.01 to ≤0.1 mg/m^3	≤0.01 mg/m^3
Gas/vapor	>1 to ≤10 ppm	>0.1 to ≤1 ppm	≤0.1 ppm
Carcinogenicity	—	—	H350, Category 1, 1A, or 1B
	—	—	H351, Category 2
Reproductive toxicity	H361, Category 2	H360, Category 1B	H360, Category 1 or 1A
Specific target organ toxicity-repeated exposure	H371, Category 2	—	H370, Category 1
	H373, Category 2	—	H372, Category 1
Genotoxicity	—	H341, Category 2	H340, Category 1, 1A or 1B
Respiratory and skin sensitization	H317, Category 1B (skin)	H317, Category 1 or 1A	—
	H335, Category 3	H334, Category 1B	H334, Category 1 or 1A
Acute toxicity	H301, Category 3	H300, Category 2	H300, Category 1
	H302, Category 4	H300, Category 2	H300, Category 1
	H331, Category 3	H330, Category 2	H330, Category 1
	H332, Category 4	H330, Category 2	H330, Category 1
	H311, Category 3	H310, Category 2	H310, Category 1
	H312, Category 4	H310, Category 2	H310, Category 1
Skin corrosion/ irritation	H315, Category 2	—	H314,Category 1, 1A, 1B, or 1C
Eye damage/ irritation	H319, Category 2, 2A or 2B	—	H318, Category 1

*Note that the following H-codes are not used for Tier 1 banding: H200s, H303, H304, H305, H313, H316, H320, H333, H336, H362, and H400s. These H-codes are either not occupationally relevant or not sufficient because they reflect oral hazards or reflect other health endpoints.

Abbreviations: mg/m^3 = milligrams per cubic meter; ppm = parts per million

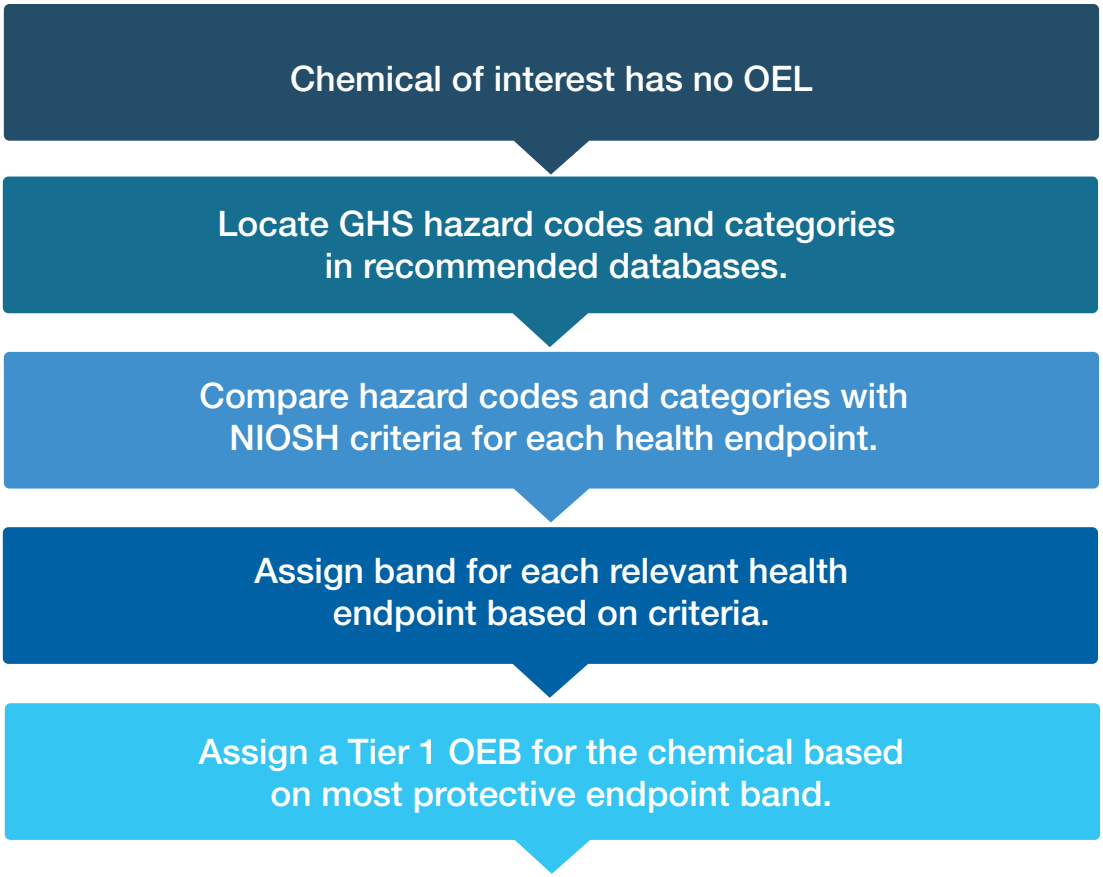

Figure 2-1. Overview for banding chemical substances in Tier 1.

2.1 GHS Hazards Statements, H-Codes, and Categories

Hazard statements, H-codes, and categories are aligned with standardized hazard criteria for toxicological endpoints defined by GHS. These endpoints are called hazard classes. The health hazard classes defined by GHS are (1) carcinogenicity, (2) reproductive toxicity, (3) specific target organ toxicity, (4) genotoxicity, (5) respiratory sensitization, (6) skin sensitization, (7) acute toxicity, (8) skin corrosion and irritation, and (9) eye damage/irritation.

GHS hazard statements are standardized phrases that capture the nature and extent of the potential risks to human health through contact with a chemical substance. A given chemical substance may have a hazard statement for one or more of these endpoints, and the statements will vary depending on the severity of the endpoint. For example, several GHS health hazard statements address the acute toxicity potentially associated with dermal exposure to a chemical substance. These statements include "May be harmful in contact with skin," "Harmful in contact with skin," "Toxic in contact with skin," and "Fatal in contact with skin."

Each hazard statement assigned to a chemical substance by GHS is accompanied by an alphanumerical H-code. Marked by simplicity and ease of use, H-codes related to health endpoints always begin with the letter H, followed by the digit 3. For example, "May be harmful in contact with skin" is coded as H313, and "Fatal in contact with skin" is coded as H310.

Under GHS, chemical substances are also assigned a hazard category. These categories compare hazard severity within a hazard class and are assigned according to specific toxicological cut-points (such as median lethal dose values for acute toxicity) or expert judgement decisions (such as for assessing the potential for human carcinogenicity). The hazard category can often provide greater distinction and more specific information than hazard statements and codes.

The full suite of GHS H-codes, statements, and hazard categories is listed in Table A3.1.2 of GHS (Rev. 5) [UNECE 2015]. As illustrated in (Table 2-1) of this document, most of these H-code and category combinations correspond to a band in the NIOSH occupational exposure banding scheme. The OSHA hazard communication standard provides detailed information and training on GHS H-codes and hazard statements [OSHA 2012].

2.2 Data Sources for GHS H-codes and Categories

A number of resources can be used to obtain hazard statements, H-codes, and categories. NIOSH recommends the following as information sources:

Annex VI to the Classification, Labelling, and Packaging of Substances and Mixtures

Annex VI is a European database of approximately 1,300 chemical substances that is part of the Classification and Labeling and Packaging of chemical substances and mixtures. This database can be found on the website of the European Chemical Agency [ECHA 2013]. Information on chemical substances and mixtures, including GHS hazard statements, H-codes, and categories, is available in Annex VI.

GESTIS Substance Database

GESTIS, a hazardous chemical substance database of German Social Accident Insurance that contains approximately 8,000 chemical substances [GESTIS 2012], is available at http://gestis-en.itrust.de/. Information in GESTIS includes toxicological data; physical and chemical properties; regulations; and hazard statements, H-codes, and categories.

Safety Data Sheets

SDSs are the primary channel through which manufacturers communicate chemical safety and health information to workers and emergency response personnel who may be exposed to hazardous chemical substances. The OSHA hazard communication standard is now aligned with the GHS, meaning that manufacturers must provide a harmonized hazard statement for each hazard class and category [OSHA 2012]. As of June 1, 2015, OSHA-compliant SDSs contain GHS hazard statements, H-codes, and categories that can be used for Tier 1 analysis (Figure 2-2).

2.3 Steps in the Tier 1 Analysis

The first step in the Tier 1 analysis is to determine whether an authoritative (i.e., government, consensus, or peer-reviewed) or reliable internal OEL is available for the chemical substance under consideration. Examples are NIOSH recommended exposure limits (RELs), OSHA PELs, American Conference of Governmental Industrial Hygienists (ACGIH®) threshold limit values

This section identifies the hazards of a chemical substance presented on the SDS and the appropriate warning information associated with the hazards. The required information consists of:

- The hazard classification of the chemical (e.g., flammable liquid, category).
- Signal word.
- Hazard statement(s).
- Pictograms or hazard symbols may be presented as graphical reproductions of the symbols in black and white or be a description of the name of the symbol (e.g., skull and crossbones, flame).
- Precautionary statement(s).
- Description of any hazards not otherwise classified.
- For a mixture that contains an ingredient(s) with unknown toxicity, a statement describing how much (percentage) of the mixture consists of ingredient(s) with unknown acute toxicity. Please note that this is a total percentage of the mixture and not tied to the individual ingredient(s).

Figure 2-2. Required elements in Section 2 of OSHA-compliant safety data sheets, as defined by the hazard communication standard (29 CFR 1910.1200(g)), revised in 2012.

(TLVs®), American Industrial Hygiene Association (AIHA)/Occupational Alliance for Risk Science workplace environmental exposure limits (WEELs), and European Union Scientific Committee on Occupational Exposure Limits (SCOELs). Current OEL information can be found on an OSHA-compliant SDS, in the NIOSH Pocket Guide to Chemical Hazards [NIOSH 2010], or any updates provided by the organization that derived the OEL being considered. If one of these OELs is available, then it is not recommended to derive an OEB. Controls should be implemented to limit worker exposure to at most the available OEL. This step is important because OEBs do not replace traditional OELs; the latter typically are based on more data, more in-depth data evaluation, and peer-review procedures. However, when authoritative OELs are not available, occupational exposure banding can be used to make decisions about worker exposure and protection if sufficient data exist.

In gathering information for Tier 1, the user should identify the H-codes and categories assigned to the agent. These are shown in the sources listed in Section 2.2 of this document. For occupational exposure banding purposes, most of the 300-level H-codes are used, because they correspond to health hazards. Some 300-level H-codes represent health effects that are not sufficient for Tier 1 banding and therefore are not included. The 300-level H-codes that are not used for banding include H303, H304, H305, H313, H316, H320, H333, H336, and H362. Some of these reflect oral hazards and others reflect health endpoints that are not informative for inhalation hazards. Furthermore, 200-level H-codes that correspond to physical hazards and 400-level H-codes that correspond to ecotoxicology are also not used for banding purposes.

Using the H-codes assigned to a given chemical substance for each toxicological endpoint, the technical criteria listed in Table 2 provide guidance on the selection of the corresponding OEB for that endpoint. The band for each health endpoint for which H-codes are available is entered into the Tier 1 worksheet. Where multiple H-codes for a single chemical substance are found and those H-codes correspond to different bands, the overall OEB is defined as the most stringent band. For example, if Tier 1 H-codes are found that correspond with band D and band E, then the chemical substance is assigned band E in Tier 1.

To assist the user in completing the Tier 1 banding process, Appendix A contains the Tier 1 criteria along with a blank worksheet that can be used to record H-codes, hazard categories, and the corresponding endpoint specific band. The most stringent of these bands is recorded at the bottom of the worksheet. This is the Tier 1 OEB for the chemical substance.

Users can also use the online occupational exposure banding e-Tool to complete the Tier 1 process. The e-Tool incorporates the occupational exposure banding process and allows users to apply toxicology and potency information to generate quantitative exposure guidance for chemical substances. For Tier 1, the e-Tool integrates the Tier 1 criteria and links the e-Tool to the GESTIS substance database, allowing users to auto-populate GHS H-codes and categories for any chemical substance found in the GESTIS database. The e-Tool also gives users the ability to manually enter Tier 1 data, using other recommended sources listed in Section 2.2. The e-Tool is an easy and efficient way for users to band a large number of chemical substances in a short time without having to rely on the paper worksheets or criteria.

2.4 Detailed Example of a Chemical Substance Banded in Tier 1 (Table 2-2)

Chloral hydrate (CAS Number: 302-17-0)

1. Select a chemical substance to evaluate.
2. Chloral hydrate (302-17-0)
3. Determine if an authoritative OEL, such as a NIOSH REL, OSHA PEL, or ACGIH TLV®, is available. If so, implement controls to limit worker exposure to that level. If not, proceed with banding process.
    A. No OEL; proceed to Tier 1 banding.
4. Determine the three-digit H-codes and hazard categories assigned to the chemical substance by GHS. These H-codes and hazard categories can be found in Annex 6 of the GHS, the GESTIS database, and updated OSHA-compliant SDSs. Note: All 300-level H-codes correspond to health hazards, 200-level H-codes correspond to physical hazards, and 400-level H-codes correspond to ecotoxicology.
    A. For chloral hydrate, the H-codes are H315, H319, and H301.
    B. The categories are Eye Irrit 2, Skin Irrit 2, and Acute Tox 3.
5. Use the Tier 1 criteria overview to determine which OEB corresponds to each of the health based (300-level) H-codes for that chemical substance. Find the H-code on the chart, and find the corresponding OEB at the top of the column. If no H-codes are available for a particular endpoint, then that endpoint cannot be banded. Note: When H-codes correspond to more than one band, the hazard category is used to determine the endpoint-specific band.
6. Assign the overall OEB for the chemical substance, based on the most stringent H-code(s), according to the following rules:
    A. If no H-codes are available for the chemical substance, do not band in Tier 1. Proceed to Tier 2.

B. The overall band in a Tier 1 process is never less stringent than band C.

C. If the most stringent H-code corresponds to bands D and E, then the hazard categories should be used to make the final determination. If the hazard category is not available, then band E should be assigned.

7. For chloral hydrate, the most stringent H-codes correspond to band C.

Table 2-2. Tier 1 example.

Chemical Name: Chloral Hydrate

CAS Number: 302-17-0

Endpoint	Hazard code	Hazard category	H-code source	Endpoint band
Carcinogenicity	None	—	—	—
Reproductive toxicity	None	—	—	—
Specific target organ toxicity	None	—	—	—
Genotoxicity	None	—	—	—
Respiratory and skin sensitization	None	—	—	—
Acute Toxicity	—	—	—	—
Inhalation	—	—	—	—
Oral	H301	Category 3	GHS	C
Dermal	None	—	—	—
Skin corrosion/irritation	H315	Category 2	GHS	C
Eye damage/irritation	H319	Category 2	GHS	C
Most stringent band				C

Notes:

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Chapter 3

The Tier 2 Occupational Exposure Banding Process—Using Information Beyond GHS

3.0 Overview

NIOSH recommends completing the Tier 2 process in all cases when sufficient data are available because it is more precise than Tier 1 and uses point-of-departure data. The one exception is that if the Tier 1 evaluation results in a band E, then Tier 2 is optional, given that band E represents the lowest exposure concentration range and a Tier 2 process would not result in a more stringent recommendation. However, completing the Tier 2 process could be beneficial even in this situation, as the user may gather more detailed chemical information and possibly move the chemical substance into a different band. Tier 2 should always be completed for chemical substances where (1) there are no GHS H-codes/statements through which a Tier 1 analysis can be achieved or (2) the outcome of the latter analysis is incomplete or uncertain, or newer information is available that more clearly reflects the health potency of the chemical substance.

The process for Tier 2 occupational exposure banding uses information and data for nine standard toxicological endpoints and/or health outcomes that are readily available from secondary sources such as agency reviews. Proprietary or in-house data that are available to the end user can also be used in the Tier 2 banding process. Endpoints used for Tier 2 evaluation are shown in Table 3-1. Sources of toxicological information have been assessed and assigned as Rank 1 (preferred sources) or Rank 2 (second-level sources). Rank 1 sources are those that are most likely to contain readily available toxicity data for the specific health endpoint. In cases where information is not found in Rank 1 sources, the user is advised to search Rank 2. It is not necessary to consult Rank 2 if appropriate data are collected from Rank 1. However, it is important to note that Rank 2 sources are just as credible as Rank 1 sources. The main difference between Rank 1 sources and Rank 2 sources is that for a specific endpoint, a user is more likely to find the relevant information in a Rank 1 source than in a Rank 2 source. Rank 1 and Rank 2 sources are identified in Table 3-2. Additionally, Tier 2 has a data-sufficiency threshold described fully later in Section 3.2.

Table 3-1. Standard toxicological endpoints/health outcomes used for Tier 2 evaluation.

Categories	
Carcinogenicity	Respiratory Sensitization
Reproductive and Developmental Toxicity	Skin Sensitization
Specific Target Organ Toxicity-Repeated Exposure (STOT-RE)	Acute Toxicity/Lethality
Genotoxicity	Skin Corrosion/Irritation
	Eye Damage/Corrosion

The toxicity information for some of the health effects listed above may be categorical in nature (e.g., presence/absence of genotoxicity or skin irritation), whereas other outcomes are expressed as quantitative information and/or potency data. When clearly specified quantitative benchmarks are available—such as median lethal doses for acute toxicity and no-observed-adverse-effect levels (NOAELs) or equivalent point-of-departure data such as benchmark dose lower confidence limit (BMDL) or benchmark concentration lower bound (BMCL) for specific target organ toxicity–repeated exposure (STOT-RE)—then they are used for a Tier 2 evaluation. The NOAEL/BMDL or NOAEL/BMCL values that are used as the basis of agency-derived toxicity benchmarks, such as the reference dose (RfD) from the U.S. EPA or minimum risk level (MRL) from the Agency for Toxic Substances and Disease Registry (ATSDR), are preferred for assessing chemical substances in Tier 2 (Rank 1 or preferred sources), when possible. (Note: The NOAEL/BMDL or in some cases lowest observed adverse effect level (LOAEL) are used in this analysis, *not* the agency RfD or MRL, because of differences in purpose and dose adjustments.) In the absence of preferred NOAEL/BMDL values from such agency-authenticated toxicity benchmarks, clearly documented NOAELs/BMDLs from one or more of a suite of designated information sources can be used (Rank 2 or second-level sources). It is also important to note that acute or single-exposure data are not used in the Tier 2 occupational exposure banding process, except in the case of lethality data for the acute toxicity endpoint. Additional consideration of acute or single exposure would require a Tier 3 analysis.

The numerical cut-points defining each OEB reflect the concentrations at which adverse effects are likely to be avoided. Earlier, unpublished versions of the NIOSH occupational exposure banding process included band-specific ranges that approximate the GHS hazard categories, but these have been refined in the current guidance by using cut-points based on exposure response analyses, comparisons of OEBs to current OELs, and professional judgement. To ensure the cut-points reflect a range of potencies, the fraction of chemical substances covered by each OEB was determined and compared to the potency distribution of a diverse set of chemical substances for some endpoints. For more detailed information about the OEB criteria, refer to the *Toxicological Endpoints and Banding Criteria Employed in the NIOSH Occupational Exposure Banding Process* (in press).

The Tier 2 process for occupational exposure banding also assesses the sufficiency of toxicity data to ensure that adequate information is available to reliably band a chemical substance. When toxicity data are present for a given endpoint, a weighted score based on that health endpoint is assigned. The scoring process yields an endpoint determinant score (EDS) for each health endpoint and a total determinant score (TDS), which is the sum of the EDSs based on the presence of data for each health endpoint. The TDS is compared to a predetermined threshold for data sufficiency (see Section 3.2). The EDS and TDS provide indications of the presence or absence of sufficient data for each specific endpoint and the overall band. The TDS threshold was developed by using professional judgment with consideration of the severity of health outcomes and the likelihood that data regarding a particular endpoint would be indicative of data sufficiency to assign a band. The EDS and TDS reflect the NIOSH decision logic behind the type of data needed to band chemical substances reliably. It informs the user whether or not there are adequate data to make a banding decision.

This document provides an overall procedure for banding a chemical substance by using the Tier 2 process, finding the information needed to band a chemical substance, and scoring the availability and sufficiency of data for banding. Additionally, to assist the user in completing the Tier 2 banding process, Appendix B contains the Tier 2 criteria along with a blank worksheet

that can be used to record the data, the sources, the EDS and TDS, and the corresponding endpoint-specific band. The most stringent of these endpoint bands is recorded at the bottom of the worksheet. This becomes the Tier 2 OEB for the chemical substance.

Users can also employ the online occupational exposure banding e-Tool (https://wwwn.cdc.gov/NIOSH-OEB/) to complete the Tier 2 process. The e-Tool automates the occupational exposure banding process and allows users to apply toxicology and potency information to generate quantitative exposure guidance for a chemical substance. For Tier 2, users can enter data from the recommended sources for each of the endpoints, and the e-Tool will automati-cally calculate the overall band as well as the TDS for the chemical substance. The e-Tool is an easy and efficient way for users to band a large number of chemical substances in a short time without having to rely on paper worksheets or manual data entry. It is important to note that the Tier 2 banding process relies on the data that are collected and recorded by the user, and thus it is recommended that a user reassess the availability of data periodically to determine if additional data might warrant a new or updated Tier 2 evaluation of a specific chemical substance.

3.1 Overall Strategy for Banding Chemical Substances in Tier 2

The overall Tier 2 process involves collecting quantitative and qualitative toxicity information on nine toxicological endpoints from NIOSH-recommended data sources (Table 3-2). These sources have been assigned as Rank 1 (preferred sources) or Rank 2 (second-level sources). If information is available in Rank 1, it is not necessary to search Rank 2 sources. The sources are also presented in Table 3-3, which allows the user to quickly identify potential data sources for each endpoint. Data can be recorded electronically via the NIOSH occupational exposure banding e-Tool or manually via the worksheets in Appendix B of this document. Endpoint-specific findings are documented in the worksheet, and the occupational exposure banding technical criteria are used to assign endpoint-specific bands and determinant scores for the presence of data. If the TDS is at least 30, indicating that sufficient data are available for banding, then the most stringent endpoint-specific band is assigned as the OEB. The e-Tool automatically calculates the TDS, or the user can calculate the TDS by adding all of the EDS values together. This process is described in Figure 3-1.

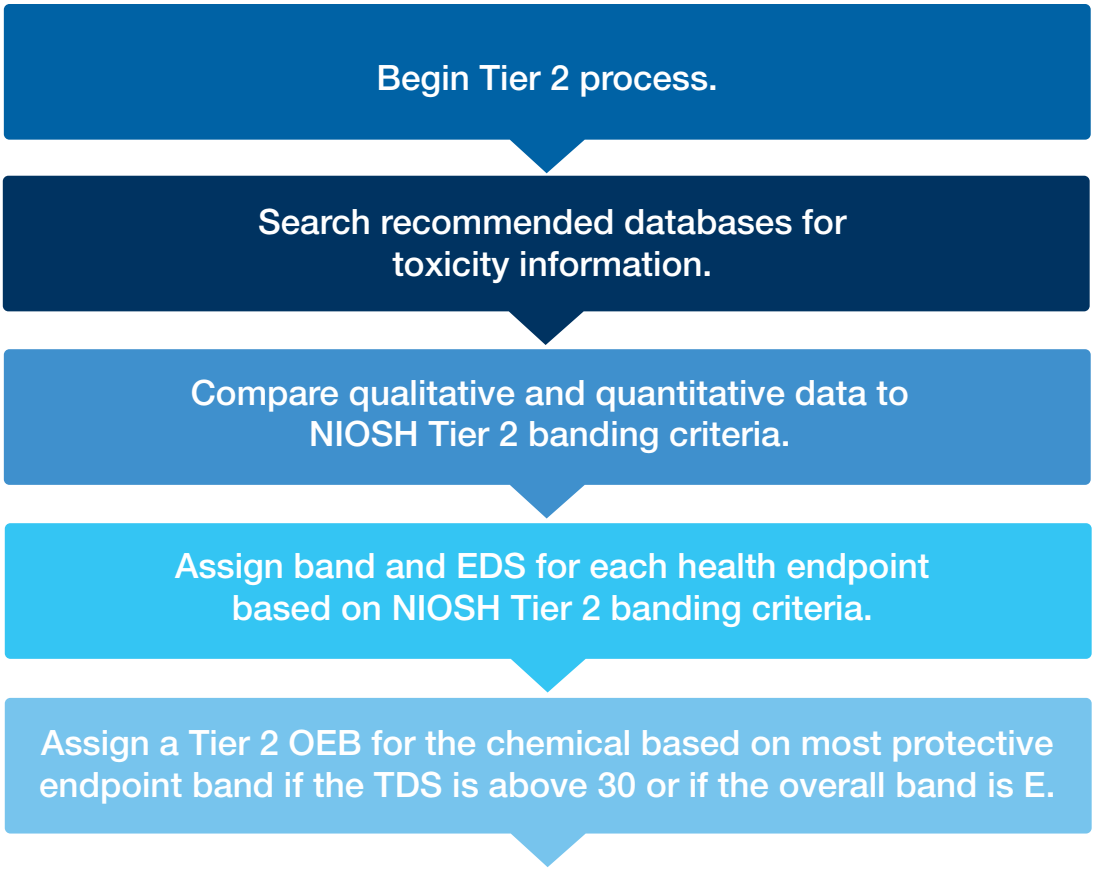

Figure 3-1. Overview of the Tier 2 process.

Table 3-2. List of information sources for banding in Tier 2.

Endpoint	Rank	Source of information	Acronym
Carcinogenicity	1	U.S. National Toxicology Program Report on Carcinogens [NTP-RoC 2016]	NTP-RoC
		U.S. EPA Integrated Risk Information System [EPA 2014]	IRIS
		International Agency for Research on Cancer [IARC 2015]	IARC
		Health Canada [Health-Canada 1996]	HC
		State of California Office of Environmental Health Hazard Assessment [CAL/EPA 2010]	Cal OEHHA

(Continued)

Table 3-2 (Continued). List of information sources for banding in Tier 2.

Endpoint	Rank	Source of information	Acronym
Reproductive Toxicity	1	U.S. National Toxicology Program [NTP 2016]	NTP
		Health Canada [Health-Canada 1996]	HC
		California Environmental Protection Agency [CAL/EPA 2016]	CalEPA
		Agency for Toxic Substances and Disease Registry Toxicological Profiles [ATSDR 2016]	ATSDR
	2	Organization for Economic Co-operation and Development [OECD 2016]	OECD
		World Health Organization International Programme on Chemical Safety [WHO-IPCS 2015]	WHO-IPCS
		U.S. EPA Office of Pesticides: Reregistration Eligibility Decision Documents [EPA 2016a]	EPA RED
		European Chemicals Agency: Registration, Evaluation, Authorisation, and Restriction of Chemicals [ECHA 2016]	REACH
Specific Target Organ Toxicity-Repeated Exposure (STOT-RE)	1	Agency for Toxic Substances and Disease Registry Toxicological Profiles [ATSDR 2016]	ATSDR
		U.S. EPA Integrated Risk Information System [EPA 2014]	IRIS
		California Environmental Protection Agency [CAL/EPA 2016]	CalEPA
		U.S. National Toxicology Program [NTP 2016]	NTP
		Health Canada [Health-Canada 1996]	HC
		European Chemicals Agency: Registration, Evaluation, Authorisation, and Restriction of Chemicals [ECHA 2016]	REACH
	2	Organization for Economic Co-operation and Development [OECD 2016]	OECD
		World Health Organization International Programme on Chemical Safety [WHO-IPCS 2015]	WHO-IPCS

(Continued)

Table 3-2 (Continued). List of information sources for banding in Tier 2.

Endpoint	Rank	Source of information	Acronym
Genotoxicity	1	U.S. National Toxicology Program [NTP 2016]	NTP
		Agency for Toxic Substances and Disease Registry Toxicological Profiles [ATSDR 2016]	ATSDR
		U.S. National Toxicology Program Report on Carcinogens [NTP-RoC 2016]	NTP-RoC
		World Health Organization International Programme on Chemical Safety [WHO-IPCS 2015]	WHO-IPCS
	2	Hazardous Substance Data Bank [HSDB 2016]	HSDB
		European Chemicals Agency: Registration, Evaluation, Authorisation, and Restriction of Chemicals [ECHA 2016]	REACH
Respiratory Sensitization	1	Organization for Economic Co-operation and Development [OECD 2016]	OECD
		European Chemicals Agency: Registration, Evaluation, Authorisation and Restriction of Chemicals [ECHA 2016]	REACH
		World Health Organization International Programme on Chemical Safety [WHO-IPCS 2015]	WHO-IPCS
	2	Agency for Toxic Substances and Disease Registry Toxicological Profiles [ATSDR 2016]	ATSDR
		U.S. EPA Integrated Risk Information System [EPA 2014]	IRIS
		Association of Occupational and Environmental Clinics [AOEC 2016]	AOEC
Skin Sensitization	1	NIOSH Skin Notation Profiles [NIOSH 2009b]	SK Profiles
		European Chemicals Agency: Registration, Evaluation, Authorisation, and Restriction of Chemicals [ECHA 2016]	REACH
		Organization for Economic Co-operation and Development [OECD 2016]	OECD
		World Health Organization International Programme on Chemical Safety [WHO-IPCS 2015]	WHO-IPCS
	2	Hazardous Substance Data Bank [HSDB 2016]	HSDB

(Continued)

Table 3-2 (Continued). List of information sources for banding in Tier 2.

Endpoint	Rank	Source of information	Acronym
Acute Toxicity	1	National Library of Medicine ChemID Plus [ChemID 2016]	ChemID Plus
		U.S. EPA Superfund Chemical Data Matrix [EPA 2016b]	EPA SCDM
		Pesticide Properties Database [PPDB 2007]	PPDB
		World Health Organization International Programme on Chemical Safety [WHO-IPCS 2015]	WHO-IPCS
		Hazardous Substance Data Bank [HSDB 2016]	HSDB
	2	Agency for Toxic Substances and Disease Registry Toxicological Profiles [ATSDR 2016]	ATSDR
Skin Corrosion/ Irritation	1	NIOSH Skin Notation Profiles [NIOSH 2009b]	SK Profiles
		World Health Organization International Programme on Chemical Safety [WHO-IPCS 2015]	WHO-IPCS
		European Chemicals Agency: Registration, Evaluation, Authorisation, and Restriction of Chemicals [ECHA 2016]	REACH
		Organization for Economic Co-operation and Development [OECD 2016]	OECD
	2	Agency for Toxic Substances & Disease Registry Toxicological Profiles [ATSDR 2016]	ATSDR
		U.S. EPA Integrated Risk Information System [EPA 2014]	IRIS
Eye Damage/ Irritation	1	Organization for Economic Cooperation and Development [OECD 2016]	OECD
		World Health Organization International Programme on Chemical Safety [WHO-IPCS 2015]	WHO-IPCS
		European Chemicals Agency: Registration, Evaluation, Authorisation, and Restriction of Chemicals [ECHA 2016]	REACH
	2	Agency for Toxic Substances and Disease Registry Toxicological Profiles [ATSDR 2016]	ATSDR
		U.S. EPA Integrated Risk Information System [EPA 2014]	IRIS

Table 3-3. Recommended sources for Tier 2 banding by endpoint.

	OEB Endpoint								
Sources	Carcinogenicity	Reproductive toxicity	STOT-RE	Genotoxicity	Respiratory sensitization	Skin sensitization	Acute toxicity	Skin corrosion/ irritation	Eye corrosion/ irritation
NTP-RoC	Rank 1	—	—	Rank 1	—	—	—	—	—
NTP	Rank 1	Rank 1	Rank 1	Rank 1	—	—	—	—	—
IRIS	Rank 1	—	Rank 1	—	Rank 2	—	—	Rank 2	Rank 2
IARC	Rank 1	—	—	—	—	—	—	—	—
HC	Rank 1	Rank 1	Rank 1	—	—	—	—	—	—
Cal OEHHA	Rank 1	—	—	—	—	—	—	—	—
ATSDR	—	Rank 1	Rank 1	Rank 1	Rank 2	—	Rank 2	Rank 2	Rank 2
CalEPA	—	Rank 1	Rank 1	—	—	—	—	—	—
OECD	—	Rank 2	Rank 2	—	Rank 1	Rank 1		Rank 1	Rank 1
Chem ID plus	—	—	—	—	—	—	Rank 1	—	—
EPA SCDM	—	—	—	—	—	—	Rank 1	—	—
PPDB	—	—	—	—	—	—	Rank 1	—	—
NIOSH SKN	—	—	—	—	—	Rank 1	—	Rank 1	—
HSDB	—	—	—	Rank 2	—	Rank 2	Rank 2	—	—
AOEC	—	—	—	—	Rank 2	—	—	—	—
WHO-IPCS	—	Rank 2	Rank 2	Rank 1	Rank 1	Rank 1	Rank 1	Rank 1	Rank 1
REACH	—	Rank 2	—	Rank 2	Rank 1	Rank 1		Rank 1	Rank 1
EPA RED	—	Rank 2	Rank 2	—	—	—	—	—	—

3.2 Assessing Data Sufficiency for Banding in Tier 2: The Total Determinant Score

A chemical substance's TDS is a quantitative measure of data sufficiency for banding in Tier 2. The TDS is the end product of a scoring system based on the availability of quantitative and/or categorical information on the entire range of toxicological outcomes. The TDS also reflects the NIOSH decision logic behind the type of data needed to band chemical substances reliably.

A Tier 2 evaluation for banding purposes is potentially more discriminating than that based on GHS statements and H-codes and could result in a chemical substance being moved from the band selected in the Tier 1 evaluation. Assessing the sufficiency of information is desirable in Tier 2 to avoid overreliance on an inadequate or limited data set that may not reflect the potential health hazard that occupational exposure to a chemical substance represents.

A numerical scheme for data adequacy is used to evaluate chemical substances with different combinations of toxicological outcomes and available data, as shown in Table 3-4.

Table 3-4. Assigned scores for the presence of toxicological endpoints encountered in the Tier 2 evaluation.

Toxicological endpoint	Endpoint determinant score (EDS)
Carcinogenicity	Qualitative = 20 or 30 Quantitative = 30
Reproductive and Developmental Toxicity	30
Specific Target Organ Toxicity-Repeated Exposure	30
Genotoxicity	5
Respiratory Sensitization	10
Skin Sensitization	5
Acute Toxicity/Lethality	5
Skin Corrosion/Irritation	5
Eye Damage/Irritation	5
Data Sufficiency/Total Determinant Score (TDS)*	30/125

*The minimum TDS criteria are waived if any of the endpoint bands are E. In that case, the chemical is assigned an overall band E, regardless of TDS.

Technical Approach

Individual scores are assigned to chemical substances for the presence of determinant-specific information. The individual score for a given health endpoint is referred to as the EDS. The TDS, which is the sum of the EDS values, is then compared to a predetermined numerical threshold (30 points). This threshold is a professional judgment on the minimum amount of information for assigning a chemical substance to a band in Tier 2 with reasonable reliability.

As shown in Table 3-4, different scores are used for the presence of data on different toxicological outcomes. These EDS values represent weights for the relative importance and severity of the toxicological outcomes under consideration, with greater weight (higher EDS) given to endpoints typically associated with chronic exposure compared to endpoints typically associated with short-term exposure. Thus, the presence of cancer data and quantitative data on systemic toxicological outcomes score higher than acute or short term health effects data, such as eye irritation. Recognizing this disparity, the scheme assigns to a chemical substance an EDS of 30 for the availability of quantitative data on cancer or systemic toxicity to target organs such as the liver and kidney. In contrast, a score of 5 is assigned for reversible or otherwise less severe toxicological outcomes to the overall health of an exposed individual or less reliable/more variable indices of chemical hazard through occupational exposure (for example, acute toxicity).

As shown in Table 3-4, the data-sufficiency threshold of 30 (out of a maximum possible TDS of 125) was selected empirically to increase the likelihood that sufficient data from at least one of the more chronic endpoints, specifically, cancer, STOT-RE, and/or reproductive health, was present. To reach a TDS of 30, data from at least one chronic, subchronic, or reproductive endpoint is needed, ensuring that banding is not based solely on acute health endpoints. A chemical-specific TDS of less than 30 would indicate that the data are scarce and do not support banding in Tier 2. In such circumstances, a Tier 3 evaluation would be necessary or users can default to a Tier 1 band if available. A TDS of 30 or more would justify choosing the most stringent band from all of the endpoints evaluated as the Tier 2 outcome. The band obtained in Tier 2 would supersede the band obtained in Tier 1, whether it is a more or less stringent band. This is because the Tier 2 band would be supported by data from approved sources. The minimum TDS criteria are waived if any of the endpoint bands are E. In that case, the chemical substance is assigned an overall band E, regardless of TDS. The rationale for this is that even when very limited data are available, indications of high toxicity should alert the user to adopt the most stringent band until additional toxicity data are generated.

Practical Considerations: The Endpoint Determinant Score

The concept of an EDS has been introduced to avoid counting studies regardless of endpoint studied. For example, if a chemical substance has nine studies spread across all nine endpoints, then the TDS would be 125 (30 for cancer + 30 for STOT-RE + 30 for reproductive + 5 for genotoxicity + 10 for respiratory sensitization + 5 for acute toxicity + 5 for eye damage + 5 for skin irritation + 5 for skin sensitization). However, if a chemical substance has nine studies but eight are of acute toxicity (median lethal dose [LD_{50}] or median lethal concentration [LC_{50}]) and one is of genotoxicity, then the TDS would be 10 (5 for acute toxicity and 5 for genotoxicity). This allows consideration of the type of data rather than the number of studies in order to assess the robustness of the database supporting the overall band. The Tier 2 checklist shows how this information should be recorded (Table 3-5).

Special TDS Considerations for Carcinogenicity Data

If quantitative cancer information for a chemical substance is available, it will take precedence over qualitative or categorical data. An EDS of 30 is assigned for any type of quantitative cancer data described in the NIOSH criteria (SF, TD_{05}, TC_{05}, etc.). In the absence of quantitative data, categorical information or weight-of-evidence determinations are used. An EDS of 30 is assigned whenever categorical information results in a band E or band A designation. When categorical information results in band D, an EDS of 20 is assigned, indicating that the information supporting a cancer endpoint is not as robust.

Table 3-5. Checklist for Tier 2 banding.

Chemical name: **CAS number:**			
Endpoint	**Data**	**EDS**	**Endpoint Band**
Carcinogenicity	Source:		
Reproductive toxicity	Source:		
Specific Target Organ Toxicity-Repeated Exposure (STOT-RE)	Source:		
Genotoxicity	Source:		
Respiratory sensitization	Source:		
Skin sensitization	Source:		
Acute toxicity	Source:		
Skin corrosion/irritation	Source:		
Eye damage/irritation	Source:		
OVERALL Tier 2 BAND		TDS =	

The minimum TDS criteria are waived if any of the endpoint bands are E. In that case, the chemical substance is assigned an overall band E, regardless of TDS.

3.3 Banding Potentially Hazardous Chemical Substances on the Basis of Carcinogenicity

Cancer is a group of diseases that cause normal healthy cells in the body to change and grow out of control. Abnormally reproducing cells of this kind can spread throughout the body (metastasize), crowding out normal cells and tissue in the process [ACS 2013].

A carcinogen is defined [UNECE 2015] as a

> "... substance or a mixture of substances which induce cancer or increase its incidence. Substances which have induced benign and malignant tumors in well performed experimental studies on animals are considered also to be presumed or suspected human carcinogens unless there is strong evidence that the mechanism of tumor formation is not relevant for humans…More explicitly, chemical substances are defined as carcinogenic if they induce tumors, increase tumor incidence and/or malignancy or shorten the time to tumor occurrence. Benign tumors that are considered to have the potential to progress to malignant tumors are generally considered along with malignant tumors. Chemical substances can potentially induce cancer by any route of exposure (e.g., when inhaled, ingested, applied to the skin, or injected), but carcinogenic potential and potency may depend on the conditions of exposure (e.g., route, level, pattern and duration of exposure)."

Evidence of a chemical substance's carcinogenic potential in humans may arise from studies of groups of people who have been exposed environmentally or in the workplace or from long-term studies in experimental animals.

Data Sources—Carcinogenicity

Sources for Tier 2 information on carcinogenicity are shown in Table 3-6.

Table 3-6. Information sources for carcinogenicity endpoint.

Endpoint	Rank	Source of information	Acronym
Carcinogenicity	1	U.S. National Toxicology Program Report on Carcinogens	NTP-RoC
		U.S. EPA Integrated Risk Information System	IRIS
		International Agency for Research on Cancer	IARC
		Health Canada	HC
		State of California Office of Environmental Health Hazard Assessment	Cal OEHHA

Classification Criteria—Carcinogenicity

Carcinogenicity can be assessed quantitatively or qualitatively, depending on the data available. For banding purposes, either qualitative assessments or quantitative assessments can be used, but if both are available then the band resulting from the quantitative assessment takes precedence.

Quantitative Assessment—Carcinogenicity

The quantitative assessment of carcinogenicity uses a measure of potency as a more accurate way to band chemical substances than a qualitative-only approach. Because OEBs represent concentration ranges, potency information is more desirable in terms of selecting the appropriate band. Potency data may be in the form of a slope factor (SF), an inhalation unit risk (IUR), or a tumorigenic dose (TD_{05}) or concentration (TC_{05}) associated with a 5% increase in tumor incidence or mortality. To conduct a quantitative assessment, the potency measure is converted to appropriate units (if necessary) and compared to quantitative banding criteria to select the appropriate band, as shown in Table 3-7.

Table 3-7. Criteria for carcinogenicity toxicity (quantitative analysis).

NIOSH banding criteria for carcinogenicity			
Exposure/ dosing route	**Endpoint Band C**	**Endpoint Band D**	**Endpoint Band E**
Slope Factor	<0.01 $(mg/kg\text{-}day)^{-1}$	≥0.01 to <10 $(mg/kg\text{-}day)^{-1}$	≥10 $(mg/kg\text{-}day)^{-1}$
Inhalation Unit Risk	$<3 \times 10^{-6}$ $(\mu g/m^3)^{-1}$	$\geq 3 \times 10^{-6}$ to <0.01 $(\mu g/m^3)^{-1}$	≥0.01 $(\mu g/m^3)^{-1}$
TD_{05}	>5 mg/kg-day	>0.005 to ≤5 mg/kg-day	≤0.005 mg/kg-day
TC_{05}	>16,700 $\mu g/m^3$	>5 to ≤16,700 $\mu g/m^3$	≤5 $\mu g/m^3$

Three sources, US EPA IRIS, Health Canada, and State of California Office of Environmental Health Hazard Assessment Cal-OEHHA, provide sufficient quantitative information to develop the carcinogenicity hazard band and should be used for quantitative assessment. Once a band has been selected on the basis of a potency estimate, there is no need to go to other sources listed in Table 3-6 for this analysis.

Endpoint-Specific Band Selection—Quantitative Carcinogenicity

- To band a chemical substance by using an SF or IUR, first ensure that the values are in the appropriate units or convert the values to the appropriate units.
- Compare the SF or IUR to the quantitative criteria and assign a band accordingly (Table 3-7). The band assigned on the basis of SF or IUR takes precedence over any band assigned based on a qualitative description.
- If both a SF and an IUR are available, whichever gives the more stringent band takes precedence for band selection in Tier 2. The SF and IUR represent the proportion of a population at risk for developing cancer and the higher values are more potent.
- If a TD_{05} is available for the agent, ensure that the units are in milligrams per kilogram per day (mg/kg-day).
- If a TC_{05} is available for the agent, ensure that the units are micrograms per cubic meter ($\mu g/m^3$).
- If quantitative carcinogenicity data are available, assign an EDS of 30 points.

Qualitative Assessment—Carcinogenicity

In the qualitative assessment, sources in Table 3-2 should be checked for carcinogen classifications and assessed by using the criteria in Table 3-7. Special guidance for each of these sources follows.

Table 3-8. Criteria for carcinogenicity toxicity (qualitative analysis).

Classification	Endpoint Band	Endpoint determinant score
National Toxicology Program Report on Carcinogens		
Known to be human carcinogen	E	30
Reasonably anticipated to be human carcinogen	E	30
Environmental Protection Agency Integrated Risk Information System		
Group A (human carcinogen)	E	30
Carcinogenic to humans	E	30
Group B1 (probable human carcinogen)	E	30
Group B2 (probable human carcinogen)	E	30
Likely to be carcinogenic to humans	E	30
Group C (possible human carcinogen)	D	20
Suggestive evidence of carcinogenic potential	D	20
Group D (not classifiable as to human carcinogenicity)	No band	0
Data are inadequate for an assessment of carcinogenic potential	No band	0
Group E (evidence of non-carcinogenicity for humans)	A	30
Not likely to be carcinogenic to humans	A	30
International Agency for Research on Cancer		
Group 1 (carcinogenic to humans)	E	30
Group 2A (probably carcinogenic to humans)	E	30
Group 2B (possibly carcinogenic to humans)	E	30
Group 3 (not classifiable as to its carcinogenicity to humans)	No band	0
Group 4 (probably not carcinogenic to humans)	A	30
State of California Office of Environmental Health Hazard Assessment		
Type of toxicity = cancer	E	30

Endpoint-Specific Band Selection—Qualitative Carcinogenicity

National Toxicology Program Report on Carcinogens

- The most recent National Toxicology Program (NTP) Report on Carcinogens (RoC) can be searched for the chemical substance of interest. If NTP has classified the chemical substance as either *known to be human carcinogen or reasonably anticipated to be human carcinogen,* assign an EDS of 30 and band E.
- If neither of these designations is located, this source does not have information about the carcinogenicity of this chemical substance. In that case, the EDS is 0. No band is assigned, and the next source is assessed.

Environmental Protection Agency Integrated Risk Information System (IRIS)

- The US EPA IRIS carcinogen classification can be checked on the US EPA IRIS website. The weight of evidence (WOE) descriptor should be evaluated. It is important to note that there is not a one-to-one correspondence between EPA and IARC cancer classification, and thus the descriptors are assigned different EDS scores for similar descriptors. Please see individual agency criteria classification for additional information and guidance.
- If the WOE descriptor is one of the following:
  - Group A (human carcinogen)
  - Carcinogenic to humans
  - Group B1 (probable human carcinogen)
  - Likely to be carcinogenic to humans
  - Group B2 (probable human carcinogen)

  then assign an EDS of 30 and band E.
- If the WOE descriptor is one of the following:
  - Group C (possible human carcinogen)
  - Suggestive evidence of carcinogenic potential

  then assign an EDS of 20 and band D. For this group, US EPA found some evidence of carcinogenicity but the data were not sufficiently robust to have high confidence in the assessment. Because of the low level of confidence in this grouping, an EDS of 20 is assigned.
- If the WOE descriptor is
  - Group D (not classifiable as to human carcinogenicity or data are inadequate for an assessment of carcinogenic potential)

  then assign an EDS of 0. No band is assigned on the basis of this source. For this group, the EPA did not find enough information to assess the carcinogenicity of the chemical substance.
- If the WOE descriptor is
  - Group E (evidence of noncarcinogenicity for humans or not likely to be carcinogenic to humans)

  then assign an EDS of 30 and band A. For this group, EPA found that the data were sufficiently robust to conclude that the chemical substance is not likely to be a human carcinogen.

International Agency for Research on Cancer

- The IARC carcinogen classification can be found on the IARC monograph website (Table 3-6). Check the corresponding IARC monograph website for any additional information. It is important to note that there is not a one-to-one correspondence between IARC and EPA cancer classifications, and thus the descriptors are assigned different EDS scores for similar descriptors. Please refer to individual agency criteria classifications for additional information and guidance.
- If IARC has classified the chemical substance as
  - Group 1 (carcinogenic to humans), Group 2A (probably carcinogenic to humans) or Group 2B (possibly carcinogenic to humans), assign an EDS of 30 and endpoint band E.
  - Group 3 (not classifiable as to its carcinogenicity to humans) or IARC has not classified the chemical substance, then move to the next source. No EDS is assigned.
  - Group 4 (probably not carcinogenic to humans), assign an EDS of 30 and endpoint band A.

State of California Office of Environmental Health Hazard Assessment (CalOEHHA)

- CalOEHHA lists chemical substances known to cause cancer as part of its Proposition 65 list. The list is available online and can be searched by name or Chemical Abstract Service (CAS) number. If the chemical substance has the designation "cancer" under the heading Type of Toxicity, then assign a determinant score of 30 and endpoint band E.

Health Canada

- Health Canada does not independently assess carcinogenicity with WOE descriptors. Instead, they report carcinogenicity designations from ACGIH®, Cal/EPA, the European Union, IARC, and NTP. This source should not be consulted for qualitative data. Use this source for quantitative carcinogenicity information only.

3.4 Banding Potentially Hazardous Chemical Substances on the Basis of Reproductive Toxicity

Reproductive toxicity includes "adverse effects on sexual function and fertility in adult males and females, as well as developmental toxicity in the offspring" [UNECE 2015]. As discussed in the NTP monograph *Specifications for the Conduct of Studies to Evaluate the Reproductive and Developmental Toxicity of Chemical, Biological and Physical Agents in Laboratory Animals for the National Toxicology Program* [NTP 2011], data derived from developmental and reproductive studies focus on three main topics: (1) fertility and reproductive performance, (2) prenatal development, and (3) postnatal development.

Endpoints of reproductive toxicity include dose-related impacts on fertility and fecundity, as well as any changes to interrelated reproductive parameters that may suggest an agent-related perturbation of reproductive function. These could include effects on estrous cyclicity, sperm parameters, litter observations, histopathology of reproductive organs at term, and reproductive indices and performance. Indicators in the latter category might include compound-related changes to the weights of uterus and placenta and differences in the numbers of corpora lutea, implantations, resorptions, and dead and living fetuses.

For developmental toxicity, indicators of chemical substance–related impacts to the fetus would be sex ratio; fetal weight and overall size; incidence of external, visceral, or skeletal malformations or variations; clinical signs; and/or other fetal changes that become evident on necropsy and histopathology.

Data Sources—Reproductive Toxicity

Sources for Tier 2 information for reproductive toxicity are shown in Table 3-9.

Table 3-9. Information sources for reproductive toxicity endpoint.

Endpoint	Rank	Source of information	Acronym
Reproductive Toxicity	1	U.S. National Toxicology Program	NTP
		Health Canada	HC
		California Environmental Protection Agency	CalEPA
		Agency for Toxic Substances and Disease Registry Toxicological Profiles	ATSDR
	2	Organization for Economic Co-operation and Development	OECD
		World Health Organization International Programme on Chemical Safety	WHO-IPCS
		U.S. EPA Office of Pesticides: Reregistration Eligibility Decision Documents	EPA RED
		European Chemicals Agency: Registration, Evaluation, Authorisation, and Restriction of Chemicals	REACH

Classification Criteria—Reproductive Toxicity

For a Tier 2 assessment, studies in experimental animals designed to observe reproductive and developmental toxicity provide relevant data for banding chemical substances for this endpoint. The occupational exposure banding assignments for reproductive toxicity are based on NOAELs/BMDLs (Table 3-10). The criteria use dose-response information and provide a quantitative basis for assigning a band for this endpoint. NIOSH established the banding criteria for developmental and reproductive toxicity by dividing NOAELs/BMDLs by an uncertainty factor of 900. This represents 10 for interspecies variability, 10 for intraspecies variability, 3 for subchronic to chronic extrapolation, and an additional 3 for the seriousness of reproductive and developmental toxicity as a health endpoint. A sample of 284 NOAELs for reproductive and developmental toxicity was evaluated to ensure the resulting bands were distributed appropriately across the banding criteria.

When using the NIOSH Occupational Exposure Banding Process, NOAEL and/or BMDL values should be derived from authoritative reviews of studies featuring oral, dermal, and/or inhalation exposures in experimental animals (or humans). The studies considered should be well conducted and documented, such as those that use internationally accepted test methods like the OECD Guidelines for the Testing of Chemical Substances and EPA Good Laboratory Practices (GLP) and assess one or more of the following endpoints:

1. Developmental toxicity
2. Perinatal and postnatal toxicity
3. One-generation or two-generation toxicity
4. Reproductive/developmental toxicity
5. Combined repeated-dose toxicity studies with reproduction/developmental toxicity
6. Short-term or long-term repeated-dose toxicity (i.e., studies that have reported adverse effects or changes that have been judged likely to impair reproductive function and that occur in the absence of significant generalized toxicity).

Table 3-10. Criteria for reproductive toxicity endpoint.

NIOSH Banding Criteria for Reproductive Toxicity (NOAEL/BMDL/BMCL)					
Exposure/ dosing route	**Endpoint Band A**	**Endpoint Band B**	**Endpoint Band C**	**Endpoint Band D**	**Endpoint Band E**
Oral, Dermal	>300 mg/ kg-day	>30 to ≤300 mg/kg-day	>3 to ≤30 mg/ kg-day	>0.3 to ≤3 mg/kg-day	≤0.3 mg/ kg-day
Inhalation (gases/ vapors)	>10,000 ppm	>1,000 to ≤10,000 ppm	>100 to ≤1,000 ppm	>10 to ≤100 ppm	≤10 ppm
Inhalation (dust/ particles)	>10,000 µg/ m^3	>1,000 to ≤10,000 µg/ m^3	>100 to ≤1,000 µg/m^3	>10 to ≤100 µg/m^3	≤10 µg/m^3
Oral, Dermal	>300 mg/ kg-day	>30 to ≤300 mg/kg-day	>3 to ≤30 mg/kg-day	>0.3 to ≤3 mg/kg-day	≤0.3 mg/ kg-day

Note: The banding criteria for each endpoint were developed independently of each other, based on existing data or widely-accepted practice. The result is that exposure thresholds associated with each band will be unique to the endpoint and concentrations will not be directly comparable across endpoints. This does not impact the utility or usability of these criteria and is consistent with the screening purpose of this tool.

Approach to Data Selection—Reproductive Toxicity

When reviews by authoritative bodies (such as NTP monographs or ATSDR toxicology profiles) are available, those sources are preferred as a source of NOAELs/BMDLs. In the absence of NOAELs and BMDLs, a LOAEL may be used (see Table 3-9 for data sources). The following approach is suggested.

Endpoint-Specific Band Selection—Reproductive Toxicity

The following steps are suggested for assigning a band:

1. If route-specific NOAELs/BMDLs are available, use them directly to assign an endpoint band according to the criteria (Table 3-10).
2. If a LOAEL but no NOAEL is available for any route, divide the LOAEL by 10 to convert the LOAEL to a NOAEL equivalent [Dankovic et al. 2015].
3. If multiple NOAELs/BMDLs are available for a given route of exposure, the lowest NOAEL/BMDL is used for that route.
4. When NOAELs/BMDLs are available for multiple exposure routes, assign the most stringent band as the overall band for the reproductive toxicity of the chemical substance.
5. If no route-specific NOAELs/BMDLs (or LOAELs) are available, criteria for the reproductive toxicity endpoint are not met and no reproductive toxicity-specific band is assigned for this chemical substance.

Endpoint Determinant Score—Reproductive Toxicity

The determination of the availability of adequate data in authoritative reviews to support banding decisions is based on (1) quantitative epidemiological information on the reproductive effects of toxicants in exposed humans and/or (2) experimental data on these outcomes in animals. If a NOAEL/BMDL or LOAEL is available, an EDS of 30 is assigned to indicate sufficient information is available for banding in Tier 2. The presence of multiple acceptable NOAEL/BMDL or LOAEL measures indicates assignment of a score of 30. If there are no available data for reproductive toxicity, then no band is assigned, and the EDS is 0. This score is based on the availability of the information, regardless of the outcome of the test or observation (positive/negative).

Unit Conversions for Inhalation Data—Reproductive Toxicity

The U.S. EPA [EPA 1994] provides a detailed explanation of how the ideal gas law is used to convert concentrations of gases and vapors expressed in ppm to mg/m^3 and vice versa. The formula for conversion and an example is provided below for reference.

- At 25°C and 760 mm Hg, 1 gram per mole of a perfect gas or vapor occupies 24.45 L; under these conditions, the conversion becomes
  - mg/m^3 = (ppm × molecular weight [MW])/24.45
- Converting concentrations expressed in mg/m^3 to ppm would require inverting the above calculation as follows:
  - ppm = $(mg/m^3 \times 24.45)/MW$

For example, if the chemical substance of concern was chloral hydrate (CAS number 302-17-0) with molecular weight of 165.39 grams per mole, convert a concentration of 20 ppm to mg/m^3 as follows:

- Formula: mg/m^3 = (ppm x MW)/24.45
  - (20 ppm x 165.39 g/mol)/(24.45 L/mol) = 135.29 mg/m^3

And conversely, convert a concentration of 100 mg/m^3 to ppm as follows:

- Formula: ppm = (mg/m^3 x 24.45)/MW
  - (100 mg/m^3 x 24.45 L/mol)/(165.39 g/mol) = 14.8 ppm

3.5 Banding Potentially Hazardous Chemical Substances on the Basis of Specific Target Organ Toxicity

Specific target organ toxicity (STOT) following repeated exposure is the consequence of a "consistent and identifiable toxic effect in humans, or, in experimental animals, toxicologically significant changes which have affected the function or morphology of a tissue/organ, or have produced serious changes to the biochemistry or hematology of the organism, and these changes are relevant to human health" [UNECE 2015].

Examples of toxicological data applicable to the specific target-organ toxicity, repeated exposure (STOT-RE), endpoint are (1) irreversible gross or histopathological changes to major target organs such as the liver and kidney, (2) dose-related trends in absolute or relative organ weights, (3) consistent changes to hematological parameters, and (4) persistent alterations in those clinical chemistry parameters that reflect physiological impairment to one or more target organs. Items in the latter category might include elevations in the serum concentrations of urea nitrogen or creatinine (indicative of damage to the kidneys) or increases in the activities of those enzymes (such as alanine aminotransferase, aspartate aminotransferase, or gamma glutamyl transferase) that are thought to reflect the functional activity of the liver.

Data Sources—STOT-RE

Sources for Tier 2 information for STOT-RE are shown in Table 3-11.

Table 3-11. Information sources for Specific Target Organ Toxicity-Repeated Exposure (STOT-RE) endpoint.

Endpoint	Rank	Source of information	Acronym
Specific Target Organ Toxicity-Repeated Exposure (STOT-RE)	1	Agency for Toxic Substances and Disease Registry Toxicological Profiles	ATSDR
		U.S. EPA Integrated Risk Information System	IRIS
		California Environmental Protection Agency	CalEPA
		U.S. National Toxicology Program	NTP
		Health Canada	HC
	2	European Chemicals Agency: Registration, Evaluation, Authorisation, and Restriction of Chemicals	REACH
		Organization for Economic Co-operation and Development	OECD
		World Health Organization International Programme on Chemical Safety	WHO-IPCS

Classification Criteria – STOT-RE

For a Tier 2 assessment, human or animal data are needed for assigning a STOT-RE band to a chemical substance. These data are typically available from authoritative reviews conducted by governmental, national, international, and professional agencies throughout the world. These agencies have published RfDs and RfCs, minimal risk levels, acceptable daily intakes, tolerable daily intakes or concentrations (TDIs or TDCs), tolerable intakes (TIs) or tolerable concentrations, etc. These values are based on target organ toxicity information and criteria specific to the organization that developed them. These reference doses/concentrations are usually derived from NOAELs/BMDLs or LOAELs (when NOAELs/BMDLs are not available) that are relevant for the STOT-RE classification. The NOAELs/BMDLs used by the agency to derive the agency recommendations should be used as the quantitative basis for assigning the band for this endpoint. If the reference dose is based on something other than STOT-RE (for instance, reproductive toxicity), then the NOAEL/BMDL or LOAEL used to derive the reference dose should not be used for banding for the STOT-RE endpoint. Instead, those data should be used for the relevant health endpoint.

NIOSH established the banding criteria for STOT-RE by dividing NOAELs/BMDLs by an uncertainty factor of 300. This represents 10 for interspecies variability, 10 for intraspecies variability, and 3 for subchronic to chronic extrapolation. A sample of 266 NOAELs for STOT-RE was evaluated to ensure the resulting bands were distributed appropriately across the banding criteria.

The user will assign a band for STOT-RE based on the NOAEL/BMDL (or adjusted LOAEL, if necessary) that is listed in the NIOSH criteria, as shown in Table 3-12. The criteria are based on dose/concentrations from standard 90-day toxicity studies conducted on rats. Similar to the reproductive toxicity endpoint, studies complying with international testing guidelines are preferred. However, availability of a reliable NOAEL/BMDL from a repeated-dose study of adequate quality in another animal model would provide a reasonable basis to assign a STOT-RE band. Similarly, a NOAEL/BMDL from a study of 28 to 90 days' duration would be acceptable for banding this endpoint, if a suitable conversion factor (see below) is applied to account for the shorter duration.

Table 3-12. Criteria for Specific Target Organ Toxicity-Repeated Exposure (STOT-RE) endpoint.

NIOSH banding criteria for Specific Target Organ Toxicity (NOAEL/BMDL/BMCL)					
Exposure/ dosing route	**Endpoint Band A**	**Endpoint Band B**	**Endpoint Band C**	**Endpoint Band D**	**Endpoint Band E**
Oral, Dermal	>1,000 mg/kg-day	>100 to ≤1,000 mg/kg-day	>10 to ≤100 mg/kg-day	>1 to ≤10 mg/kg-day	≤1 mg/kg-day
Inhalation (dust/ particles)	>30,000 µg/m^3	>3,000 to ≤30,000 µg/m^3	>300 to ≤3,000 µg/m^3	>30 to ≤300 µg/m^3	≤30 µg/m^3
Inhalation (gases/ vapors)	>30,000 ppm	>3,000 to ≤30,000 ppm	>300 to ≤3,000 ppm	>30 to ≤300 ppm	≤30 ppm

- The band criteria for each endpoint were developed independently of each other, based on existing data or widely accepted practice. The result is that exposure thresholds associated with each band will be unique to the endpoint, and concentrations will not be directly comparable across endpoints. This does not impact the utility or usability of these criteria and is consistent with the screening purpose of this tool.
- Multiple NOAELs/BMDLs for a chemical substance may be available. The value selected for banding should be the NOAEL/BMDL used by the agency as the basis for the reference dose/concentration.

Approach to Data Selection—STOT-RE

When dose-response information and target organ toxicity NOAELs/BMDLs (or adjusted LOAELs) are available from Rank 1 sources (Table 3-11), the user should identify and use, for each route, the single NOAEL/BMDL that is the most stringent. The applicable NOAEL/BMDL is compared to the NIOSH criteria (Table 3-12), and the most stringent band is assigned as the endpoint band.

In the absence of Rank 1 data, there are other sources of STOT-RE information (e.g., authoritative compilation of studies such as Screening Information Dataset, REACH) from which endpoint-specific NOAELs/BMDLs may be obtained (Rank 2).

Endpoint-Specific Band Selection—STOT-RE

Human data from repeated exposures are the preferred source of evidence for this endpoint and the associated bands. However, because human data are not generally available, data from standard 28-day, 90-day, or lifetime studies (up to 2 years) in rats and other experimental animals are more likely to provide information for this endpoint. More specifically, NOAELs/BMDLs identified in experimental animals following oral, dermal, and inhalation exposures are used to derive the endpoint specific band.

As in the reproductive toxicity endpoint, adjustments may be needed before using STOT-RE data to assign an endpoint band. Depending on study design, a duration-adjustment may be necessary. If 90-day or longer-duration NOAELs/BMDLs are available, then these values are used directly to assign a band for a chemical substance. If a NOAEL/BMDL is from a 28- to 89-day exposure, this should be divided by a factor of three to derive a NOAEL/BMDL equivalent to a 90-day exposure [Dankovic et al. 2015]. The resulting value is used to assign a band. A LOAEL-to-NOAEL adjustment also may be required. If a LOAEL rather than a NOAEL is available, then the LOAEL is divided by 10 to convert the LOAEL to a NOAEL equivalent.

If multiple NOAELs/BMDLs (or adjusted LOAELs) are available for any route of exposure, the lowest value is used for that route. When NOAELs/BMDLs (or adjusted LOAELs) are available for multiple routes of exposure (e.g., oral, dermal, inhalation) and route-specific bands are assigned, the overall STOT-RE band is represented by the most stringent band.

Endpoint Determinant Score—STOT-RE

The NOAEL/BMDL, which serves as the basis for the recommendation, provided in authoritative reviews can be based on (1) quantitative epidemiological information on STOT-RE endpoints in exposed humans and/or (2) experimental data on these outcomes in experimental animals.

If a NOAEL/BMDL is available, an EDS of 30 is assigned, indicating sufficient information is available for banding the chemical substance in Tier 2. The presence of multiple NOAEL/BMDL also warrants a score of 30. If STOT-RE data are not available, then no band can be assigned, and the EDS is 0. As with the other endpoints, this score is assigned based on the availability of the information, irrespective of the outcome of the test or observation (positive/negative).

3.6 Banding Potentially Hazardous Chemical Substances on the Basis of Genotoxicity

The genotoxicity health endpoint is related to changes in genetic material. Although genotoxicity and germ cell mutagenicity are similar terms, it is important to distinguish the two. Germ cell mutagens are chemical substances that may cause permanent heritable changes in the amount or structure of the genetic material in a germ cell. Germ cells include an ovum or sperm cell or one of its developmental precursors. Mutagenicity refers specifically to heritable changes in the DNA coding sequence, whereas genotoxicity is a more general term that includes mutations and other DNA or chromosome level changes. Thus, genotoxicity, by definition, includes mutagenicity. Chemical substances can be classified as to genotoxicity from a range of in vivo and in vitro tests [UNECE 2015].

Data Sources—Genotoxicity

Sources for Tier 2 information for genotoxicity are shown in Table 3-13.

Table 3-13. Information sources for genotoxicity endpoint.

Endpoint	Rank	Source of information	Acronym
Genotoxicity	1	U.S. National Toxicology Program	NTP
		Agency for Toxic Substances and Disease Registry	ATSDR
		U.S. National Toxicology Program Report on Carcinogens	NTP-RoC
		World Health Organization International Programme on Chemical Safety	WHO-IPCS
	2	Hazardous Substance Data Bank	HSDB
		European Chemicals Agency Registration, Evaluation, Authorisation, and Restriction of Chemicals	REACH

Classification Criteria—Genotoxicity

For Tier 2 assessments, the preference is to rely on the overall judgment on genotoxicity provided from authoritative reviews and summaries (Table 16). In authoritative reviews, agent-specific genotoxicity findings are usually gathered together in the relevant section or chapter and frequently tabulated. Where such authoritative sources are not available, data gathering for banding chemical substances according to this criterion involves searching for chemical-specific data from a range of genotoxicity tests.

Table 3-14. Criteria for genotoxicity endpoint.

NIOSH banding criteria for genotoxicity		
Endpoint Band A	**Endpoint Band C**	**Endpoint Band E**
Negative results	Mixed results	Positive results

Approach to Data Selection—Genotoxicity

Substances with demonstrable genotoxic properties have been subdivided into categories according to the available evidence. For example, chemical substances for which positive evidence is available from human epidemiological studies may be regarded as substances known to be genotoxic. In practice, data for few chemical substances rise to this level of certainty, and results from a variety of alternative assays must be considered (see Table 3-15).

Table 3-15. Examples of genotoxicity tests applicable to the Tier 2 banding process.

Type of test	Examples
In vivo heritable germ cell mutagenicity tests	Rodent dominant lethal mutation test Mouse heritable translocation assay Mouse specific locus test
In vivo somatic cell mutagenicity tests	Mammalian bone marrow chromosome aberration test Mammalian erythrocyte micronucleus test
Mutagenicity tests on germ cells	Mammalian spermatogonial chromosome aberration test Spermatid micronucleus assay
Genotoxicity tests in germ cells	Sister chromatid exchange analysis in spermatogonia Unscheduled DNA synthesis test in testicular cells
Genotoxicity tests in somatic cells	Liver unscheduled DNA synthesis test in vivo Mammalian bone marrow sister chromatid exchange
In vitro mutagenicity tests	In vitro mammalian chromosome aberration test In vitro mammalian cell gene mutation test Bacterial reverse mutation (Ames) test

Source: [UNECE 2015].

The process of reaching conclusions regarding genotoxicity potential is challenging, because the many different types of assays do not all measure the same aspects of alterations in genetic material. For example, a chemical substance that causes small changes in the DNA sequence at a single point may not show any effect in assays that primarily assess chromosome changes or large-scale DNA damage. Thus, the assessment of genotoxicity potential needs to consider both the nature of available assays as well as the results (positive or negative) for each assay.

Endpoint-Specific Band Selection—Genotoxicity

Based on the summary statements found in the authoritative reviews or the overall evaluation of the data, the most stringent band should be chosen. As shown in Table 17, the following criteria for assigning OEBs apply: A (negative results), C (mixed results), or E (positive results). These determinations are general in nature, and for data sets that do not provide a clear conclusion regarding genotoxicity potential, a Tier 3 evaluation performed by a toxicologist or other specialist should be considered. The following are some characteristics of data sets that provide the user the greatest confidence in the determination of genotoxicity:

- Availability of a summary statement on genotoxicity from an authoritative source
- Availability of genotoxicity data from in vivo assays and mammalian assays supported by in vitro and nonmammalian assays
- Consistent results in a diverse array of assays that evaluate different types of effects on genetic material (e.g., assays covering several rows in Table 3-15)

Endpoint Determinant Score—Genotoxicity

If acceptable data on genotoxicity are available, a score of 5 is assigned as the EDS. The presence of multiple acceptable studies also warrants a score of 5. If genotoxicity data are not available, then no band is assigned and the EDS is 0. This score is assigned on the basis of the availability of the information, irrespective of the outcome of the test or observation (positive/negative).

3.7 Banding Potentially Hazardous Chemical Substances on the Basis of Respiratory Sensitization

Sensitization can be differentiated into two subclasses: respiratory sensitization and skin sensitization. A respiratory sensitizer is "a substance that will lead to hypersensitivity of the airways following inhalation of the substance" [UNECE 2015]. This chapter discusses respiratory sensitization.

In Tier 2, respiratory sensitizers are allocated bands according to qualitative data. If epidemiological or clinical dose-response data are available for respiratory sensitization, then the resulting NOAELs/BMDLs are considered under the specific target-organ toxicity endpoint.

Data Sources—Respiratory Sensitization

Sources for Tier 2 information for respiratory sensitization are shown in Table 3-16.

Table 3-16. Information sources for respiratory sensitization endpoint.

Endpoint	Rank	Source of information	Acronym
Respiratory Sensitization	1	Organization for Economic Co-operation and Development	OECD
		European Chemicals Agency: Registration, Evaluation, Authorisation, and Restriction of Chemicals	REACH
		World Health Organization International Programme on Chemical Safety	WHO-IPCS

(Continued)

Table 3-16 (Continued). Information sources for respiratory sensitization endpoint.

Endpoint	Rank	Source of information	Acronym
	2	Agency for Toxic Substances and Disease Registry	ATSDR
		U.S. EPA Integrated Risk Information System	IRIS
		Association of Occupational and Environmental Clinics	AOEC

Classification Criteria—Respiratory Sensitization

For a Tier 2 assessment, human or animal data are needed to assign a respiratory sensitization band to a substance. These data are generally available from authoritative reviews conducted by governmental, national, international, and professional agencies, a selection of which are listed in Table 3-16.

Respiratory sensitization or respiratory allergy refers to an allergic reaction in the respiratory tract (e.g., asthma) following exposure to the chemical substance. Respiratory sensitization does not refer to irritation or damage to pulmonary tissue following chemical substance exposure. These outcomes would be considered for banding under specific target-organ toxicity after repeated exposure. According to the OSHA hazard communication standard, "sensitization includes two phases: the first phase is induction of specialized immunological memory in an individual by exposure to an allergen. The second phase is elicitation, i.e., production of a cell-mediated or antibody-mediated allergic response by exposure of a sensitized individual to an allergen." Evidence of respiratory sensitization is often based on human evidence. Frequently it is seen as asthma, but other symptoms of allergic reactions such as runny nose and watery eyes (rhinitis/conjunctivitis) and inflammation in the lungs (e.g., alveolitis) are also considered.

Generally, to assess respiratory sensitization risk, several agencies have adopted a qualitative approach as a first step. Because of lack of validated assay protocols that provide quantitative human or animal data on respiratory sensitization, GHS [UNECE 2015] has not proposed a specific quantitative potency criteria for Category 1 respiratory sensitizers. NIOSH recommends banding criteria for respiratory sensitization on the basis of qualitative criteria, as set forth in Table 3-17.

Table 3-17. Criteria for respiratory sensitization endpoint.

NIOSH banding criteria for respiratory sensitization		
Endpoint Band A	**Endpoint Band C**	**Endpoint Band E**
No evidence of respiratory sensitization	Mixed results	Positive evidence of respiratory sensitization

Approach to Data Selection—Respiratory Sensitization

Although no validated quantitative animal bioassays are currently available from which a reliable NOAEL or BMDL can be identified, inferential evidence on a chemical substance's potential to induce respiratory sensitization can be drawn from conclusions provided in reviews from recommended databases listed in Table 3-16

Endpoint-Specific Band Selection—Respiratory Sensitization

The following steps are followed to assign a band:

- Assign band E if the data sources indicate that the substance is a respiratory sensitizer.
- Assign band C if results from the data sources are mixed or the evidence is determined to be inconclusive.
- Assign band A if the data sources indicate that the substance is not a respiratory sensitizer.

Endpoint Determinant Score—Respiratory Sensitization

If acceptable data on respiratory sensitization are available, a score of 10 is assigned as the EDS. The presence of multiple acceptable studies also warrants a score of 10. If there are no available data for respiratory sensitization, then no band is assigned and the EDS is 0. This score is assigned on the availability of the information, irrespective of the outcome of the test or observation (positive/negative).

3.8 Banding Potentially Hazardous Chemical Substances on the Basis of Skin Sensitization

In addition to respiratory sensitization, the banding process evaluates a chemical substance's potential to cause skin sensitization. A skin sensitizer is "a substance that will lead to an allergic response following skin contact" [UNECE 2015].

In Tier 2, skin sensitizers are assigned to one of five endpoint bands, ranging from band E (potent sensitizers) to band A (nonsensitizers), on the basis of local lymph node assay (LLNA) EC3 value ranges or other standard assays. EC3 is defined as the effective concentration necessary to produce a stimulation index of 3 or more.

Data Sources—Skin Sensitization

Sources for Tier 2 information for skin sensitization are shown in Table 3-18.

Table 3-18. Information sources for skin sensitization endpoint.

Endpoint	Rank	Source of information	Acronym
Skin Sensitization	1	NIOSH Skin Notation Profiles	SK Profiles
		European Chemicals Agency: Registration, Evaluation, Authorisation, and Restriction of Chemicals	REACH
		Organization for Economic Co-operation and Development	OECD
		World Health Organization International Programme on Chemical Safety	WHO-IPCS
	2	Hazardous Substance Data Bank	HSDB

Classification Criteria—Skin Sensitization

Skin sensitization or skin allergy refers to an allergic reaction of the skin (e.g., allergic contact dermatitis) following exposure to the chemical substance. Skin sensitization does not refer to irritation and corrosion to skin following chemical substance exposure; these outcomes are a measure of skin corrosion and irritation that are addressed as a separate endpoint in this occupational exposure banding process. According to the OSHA hazard communication standard, "sensitization includes two phases: the first phase is induction of specialized immunological memory in an individual by exposure to an allergen. The second phase is elicitation, i.e., production of a cell-mediated or antibody-mediated allergic response by exposure of a sensitized individual to an allergen." Evidence of skin sensitization in humans is usually assessed by a diagnostic patch test. Evidence for skin sensitization in standard animal assays includes the LLNA, the guinea pig maximization test (GPMT), and the Buehler assay.

NIOSH has adapted its sensitization banding criteria from the GHS quantitative potency criteria for Category 1 (subcategories 1A and 1B) skin sensitizers. These criteria are based on human evidence, EC3 values in the mouse LLNA, and the percentage of positive animals in relation to the induction concentration tested in the guinea pig maximization test and the Buehler guinea pig test. GHS acknowledges that "human data are not generated in controlled experiments for the purpose of hazard classification but rather as part of risk assessment to confirm lack of effects seen in animal tests" [UNECE 2015]. Therefore, evidence from animal studies is often used and supplemented by observational data drawn from situations where humans have become exposed in either the workplace or the environment.

In a Tier 2 assessment, data for assigning a band for skin sensitization are gathered and evaluated from authoritative reviews. Both qualitative and quantitative criteria are outlined in Table 3-19 If LLNA EC3 values are available, then the chemical substance is assigned one of three potency bands (A, C, or E) on the basis of the associated threshold concentrations with respect to skin sensitization hazard. In the absence of LLNA EC3 values, NIOSH recommends using incidence of sensitization in relation to the induction concentration tested in GPMT and Buehler tests, based on 2012 ECHA recommendations. If no quantitative data are available, then qualitative data such as the NIOSH skin notation assignment can be used to assign a band for skin sensitization.

Table 3-19. Criteria for skin sensitization endpoint.

NIOSH banding criteria for skin sensitization			
Test Type	**Endpoint Band A**	**Endpoint Band C**	**Endpoint Band E**
EC3 (%), based on LLNA	Non-skin sensitizer	EC3 (%) ≥2.0 but ≤100 (weak to moderate skin sensitizer)	EC3 (%) ≤2.0 (strong to extreme skin sensitizer)
GPMT	No positive response or low incidence data	30% to 60% responding at >0.1% intradermal induction concentration *or* ≥30% responding at >1% intradermal induction concentration	≥30% responding at ≤0.1% intradermal induction concentration *or* ≥60 % responding at >0.1% to ≤1% intradermal induction concentration

(Continued)

Table 3-19 (Continued). Criteria for skin sensitization endpoint.

NIOSH banding criteria for skin sensitization			
Test Type	Endpoint Band A	Endpoint Band C	Endpoint Band E
Beuhler	No positive response or low incidence data	≥60% responding at >0.2 to ≤20% topical induction dose *or* ≥15% responding at >20% topical induction dose	≥15% responding at ≤0.2% topical induction concentration *or* ≥60% responding at any topical induction concentration
Qualitative	Negative results	Mixed results	Positive results *or* NIOSH SK-SEN notation*

*NIOSH SK-SEN notation is used for substances identified as caus¬ing or contributing to allergic contact dermatitis (ACD) or other immune-mediated responses, such as airway hyper-reactivity (asthma) [NIOSH 2009b].

Approach to Data Selection—Skin Sensitization

For the skin sensitization endpoint, chemical substances are assigned bands based on the LLNA EC3 value or the incidence data. The most stringent band is selected as the endpoint band. When quantitative skin sensitization data are available from more than one assay, the most stringent band is selected. If both qualitative and quantitative data are available for this endpoint, then the band resulting from the quantitative data takes precedence. Qualitative data will determine band assignments only in the absence of quantitative data, as quantitative data take precedence.

Endpoint-Specific Band Selection—Skin Sensitization

Although human data are generally preferred, quantitative data are typically not available for humans, so well-conducted quantitative assays in mice (LLNA) and guinea pigs (Buehler test and GPMT) are often the best source of data to assess skin sensitization. When authoritative organizations have summarized these types of studies, those data are preferred.

The following steps are followed for assigning a band:

- Consult authoritative reviews (Table 3-18) to identify reliable LLNA EC3 or sensitization incidence data reported in the GPMT or Buehler guinea pig test for a chemical substance. For banding purposes, these are compared to the technical criteria set forth in Table 3-19.
- Assign a band based on mouse LLNA EC3 value and/or the GPMT or Buehler test incidence data for sensitization.
- If multiple LLNA EC3 values and/or incidence data for sensitization from the GPMT or Buehler test are available, then the most stringent value or incidence data are used.
- If no quantitative EC3 value or incidence data are available, criteria for banding the skin sensitization endpoint are based on qualitative skin sensitization data gathered from the recommended sources.

- If both qualitative and quantitative data are available for this endpoint, then the band resulting from the quantitative data takes precedence.

Endpoint Determinant Score—Skin Sensitization

If acceptable data on skin sensitization are available, a score of 5 is assigned as the EDS. The presence of multiple acceptable studies also warrants a score of 5. If there are no available data for skin sensitization, no band is assigned, and the EDS is 0. This score is assigned on the availability of the information, irrespective of the outcome of the test or observation (positive/negative).

3.9 Banding Potentially Hazardous Chemical Substances on the Basis of Acute Toxicity Based on Lethality Data

Acute toxicity refers to those "adverse effects occurring following oral or dermal administration of a single dose of a substance, or multiple doses given within 24 hours, or an inhalation exposure of 4 hours" [UNECE 2013]. In the NIOSH occupational exposure banding process, only lethality data (LD_{50} or LC_{50}) are considered for this endpoint. Additional consideration of acute toxicity data may require a Tier 3 analysis. Other acute endpoints such as skin irriation/corosion and eye irritation/damage are considered separately in this banding process.

When lethality data are used for occupational exposure banding, chemical substances are assigned to one of five bands according to numerical values expressing the LD_{50} (for oral or dermal exposure) or the median lethal concentration (LC_{50}) (for inhalation exposure). The LD_{50} and LC_{50} represent the doses or concentrations that result in the death of 50% of the exposed group within an appropriate time, usually 14 days, after a single exposure.

Data Sources—Acute Toxicity

Sources for Tier 2 information for acute toxicity are shown in Table 3-20.

Table 3-20. Information sources for acute toxicity endpoint.

Endpoint	Rank	Source of information	Acronym
Acute Toxicity	1	National Library of Medicine ChemID Plus	ChemID Plus
		U.S. EPA Superfund Chemical Data Matrix	EPA SCDM
		Pesticide Properties Database	PPDB
		World Health Organization International Programme on Chemical Safety	WHO-IPCS
	2	Hazardous Substance Data Bank	HSDB
		Agency for Toxic Substances and Disease Registry	ATSDR

Classification Criteria for the Bands—Acute Toxicity

The numerical criteria (cut-points) for the LD_{50}s and 4-hour LC_{50}s are given in Table 3-21. NIOSH established the cut-points for the acute toxicity OEBs following the OSHA Hazard

Communication Standard [OSHA 2012]. The ranges comprising each band correspond to the acute toxicity classifications developed from the Globally Harmonized System of Chemical Classification and Labelling and adopted by OSHA in 2012. NIOSH evaluated 940 LD_{50} values and determined that the chemicals were distributed appropriately across the bands.

Approach to Data Selection—Acute Toxicity

Banding a chemical substance for acute toxicity in Tier 2 involves searching through NIOSH-recommended literature sources listed in Table 3-20 and recording all available LD_{50} and LC_{50} values for the chemical substance. The most stringent value by exposure route is used to determine the appropriate band according to the LD_{50}/LC_{50} technical criteria shown in Table 3-21.

Table 3-21. Criteria for the acute toxicity endpoint.

NIOSH banding criteria for acute toxicity					
Exposure/ dosing route	**Endpoint Band A**	**Endpoint Band B**	**Endpoint Band C**	**Endpoint Band D**	**Endpoint Band E**
Oral Toxicity (LD_{50}) mg/kg bodyweight	>2,000	>300 to ≤2,000	>50 to ≤300	>5 to ≤50	≤5
Dermal Toxicity (LD_{50}) mg/kg bodyweight	>2,000	>1,000 to ≤2,000	>200 to ≤1,000	>50 to ≤200	≤50
Inhalation: gases/ vapors (LC_{50}) ppm/4h	>20,000	>2,500 to ≤20,000	>500 to ≤2,500	>100 to ≤500	≤100
Inhalation: dust/particles (LC_{50}) mg/ liter/4h	>5.0	>1.0 to ≤5.0	>0.5 to ≤1.0	>0.05 to ≤0.5	≤0.05

Note: The band criteria for each endpoint were developed independently of each other, on the basis of existing data or widely accepted practice. The result is that exposure thresholds associated with each band will be unique to the endpoint, and concentrations will not be directly comparable across endpoints. This does not impact the utility or usability of these criteria and is consistent with the screening purpose of this tool.

Rules for Accepting or Rejecting Lethality Data for Band Selection—Acute Toxicity

Lethality data may be available from a variety of studies, some of which may be more reliable and relevant to banding than others. Not all LC_{50} and LD_{50} values are appropriate for banding. Use the following rules to accept or reject data points for band selection:

- Only values from studies using routinely employed experimental animals such as rats, mice, rabbits, and guinea pigs should be employed for banding. Values from species that are less likely to be appropriate models for toxicity in humans (such as chickens and frogs) should not be used for banding.

- Studies where the route of administration of the chemical substance dose was other than oral, dermal, or inhalation should not be used for banding because NIOSH has not developed criteria to consider them in Tier 2. Examples of routes of administration that should not be used are subcutaneous, intraperitoneal, and intravascular.

Other experimental conditions for which data are insufficient or inappropriate for banding purposes include the following:

- Studies where the experimental animal is not stated
- Studies where the experimental animal is described as "mammal"
- Lethality data that do not provide the median lethal dose, including but not limited to LD_{10}, or LD_{LO}
- Values preceded by a greater than (>) symbol, where the numerical value falls within the criteria for bands B–E
- Values from experiments in which more than a single dose was administered
- Values presented as a range of concentrations, where any of the numerical values in the range fall within the criteria for bands B–E, except when the range refers to separate values for males and females (e.g., LD_{50} of 2 mg/kg for males and 10 mg/kg for females reported as a range of 2–10 mg/kg). When separate values are available for males and females, the low end of the range is used for banding.

For LC_{50} values, the following additional rules apply:

Studies where the exposure duration is unknown should be rejected, because the concentrations cannot be scaled to the standard 4-hour exposure regimen. If the exposure duration is known but was other than 4 hours and less than 24 hours, the LC50 should be converted to a 4-hour equivalent. Although Haber's rule (simple proportionality) is sometimes used for these types of conversions, NIOSH recommends using the ten Berge equation [ten Berge 1986], which considers physicochemical properties that affect respiratory deposition and systemic absorption as well as concentration and exposure duration:

$$\textit{Adjusted } LC_{50} \text{ (4 hours)} = LC_{50} \text{ (t)} \times ((t/4)^{(1/n)})$$

where LC_{50} (t) = LC_{50} determined over t hours from the study being used, and *t* is the number of hours of exposure in the study being used to estimate the 4-hour equivalent value n = the ten Berge constant [ten Berge et al. 1986]. If the exposure duration is 4 hours or less, use a ten Berge constant of 1 (n = 1), and if the exposure duration is greater than 4 hours, use a ten Berge constant of 3 (n = 3).

Table 3-22 gives (1) a list of adjustment factors, (2) the resulting 4-hour LC_{50} calculated from an experimentally derived value of 100 mg/m^3 for various exposure periods, and (3) the comparable 4-hour LC_{50} values determined through the simple application of simple proportionality (Haber's rule). This duration adjustment factor example table is not specific to the physical form of the chemical substance and can be applied for dust/particles and gases/vapors.

Table 3-22. Duration adjustment factor example for acute toxicity*.

Experimental exposure duration in hours *(t)*	Median lethal exposure *(LC_{50}) (mg/m³ or ppm)*	ten Berge constant *(n)*	Adjustment factor $((t/4)^{(1/n)})$	ten-Berge derived 4-hour LC_{50} *(mg/m³ or ppm)*	Proportional 4-hour LC_{50}s by Haber's Rule *(mg/m³ or ppm)*
1	100 mg/m³	1	0.25	25	25
2	100 mg/m³	1	0.5	50	50
3	100 mg/m³	1	0.75	75	75
4	100 mg/m³	1	1	100	100
5	100 mg/m³	3	1.08	108	125
6	100 mg/m³	3	1.14	114	150
7	100 mg/m³	3	1.2	120	175
8	100 mg/m³	3	1.26	126	200
9	100 mg/m³	3	1.31	131	225
10	100 mg/m³	3	1.36	136	250

*This example uses a 4-hour LC_{50} calculated from an experimentally derived value of 100 mg/m³ for various exposure periods.

As shown in Table 3-22, for exposures longer than 4 hours, the ten Berge–derived 4-hour LC_{50} values are lower and thus more stringent than those calculated by using Haber's rule. It is important to note that this difference may affect band selection for some chemical substances.

After making appropriate conversions, the user should enter the values in the appropriate units (ppm/4 hours or milligrams per m³ of air/4 hours) according to whether the agent is a gas/vapor or dust/particles. For banding purposes, the appropriate cut-points for LC_{50} values associated with substances in different physical forms are given in Table 3-22.

Endpoint-Specific Band Selection—Acute Toxicity

When all the acceptable LD_{50} and LC_{50} data have been assembled by data source for each route (oral, dermal, inhalation), the lowest value is compared to the criteria for band selection.

Endpoint Determinant Score—Acute Toxicity

If acceptable data on acute toxicity are available, a score of 5 is assigned as the EDS. The presence of multiple acceptable studies also warrants a score of 5. If there are no available data for acute toxicity, no band is assigned, and the EDS is 0. This score is assigned on the availability of the information, irrespective of the outcome of the test or observation (positive/negative).

3.10 Banding Potentially Hazardous Chemical Substances on the Basis of Skin Corrosion or Irritation

Skin corrosion is "the production of irreversible damage to the skin; namely, visible necrosis through the epidermis and into the dermis, following the application of a test substance for up to 4 hours [UNECE 2015]." These corrosive reactions are typified by ulcer, bleeding, bloody scabs, and, at the end of a 14-day observation period, by discoloration due to blanching of the skin, complete areas of alopecia, and scars. Skin irritation is defined as "the production of reversible damage to the skin following the application of a test substance for up to 4 hours [UNECE 2015]." Direct effects on the skin can be defined as non-immune-mediated (nonallergic) adverse health effects resulting in damage or destruction of the skin localized at or near the point of contact [NIOSH 2009b]. Common manifestations of direct effects in addition to irritation/corrosion include (1) permanent pigmentation changes (i.e., bleaching or staining of the skin), (2) nonimmune phototoxic reaction, and (3) defatting that leads to greater susceptibility of the skin to toxic exposures. Many direct skin effects can affect the skin barrier integrity, resulting in an increased potential of chemical substance penetration and subsequent risk of systemic toxicity [NIOSH 2009b]. In-depth descriptions of this health endpoint, in addition to supplemental information useful for hazard characterization purposes of such direct skin effects beyond irritation and corrosion, are available in NIOSH Current Intelligence Bulletin Number 61 [NIOSH 2009b].

Data Sources—Skin Corrosion/Irritation

Sources for Tier 2 information for skin corrosion/irritation are shown in Table 3-23.

Table 3-23. Information sources for skin corrosion/irritation endpoint.

Endpoint	Rank	Source of information	Acronym
Skin Irritation	1	NIOSH Skin Notation Profiles	SK Profiles
		World Health Organization International Programme on Chemical Safety	WHO-IPCS
		European Chemicals Agency: Registration, Evaluation, Authorisation, and Restriction of Chemicals	REACH
		Organization for Economic Co-operation and Development	OECD
	2	Agency for Toxic Substances and Disease Registry	ATSDR
		U.S. EPA Integrated Risk Information System	IRIS

Classification Criteria—Skin Corrosion/Irritation

For the Tier 2 assessment, information for assigning a skin corrosion/irritation band to a substance is generally available from authoritative reviews conducted by governmental, national, international, and professional agencies, as listed in Table 3-23. NIOSH has not recommended band assignments on the basis of potency information (e.g., dose-response data, Draize scores) for the skin corrosion/irritation endpoint under Tier 2, for two reasons. First, there is substantial

disagreement among researchers on how to categorize potency and dose-response data for this endpoint [NIOSH 2009b]; second, the output of this banding process is an inhalation range (OEB). Therefore, additional information on dermal potency was not determined to be informative. Where 28-day or longer dermal dose-response data are available for irritation or other direct effects, such data may be used as part of the STOT-RE endpoint. The recommended NIOSH criteria are shown in Table 3-24 to assign bands for skin corrosion/irritation. NIOSH notes that the occupational exposure banding process does not assign a separate NIOSH skin notation for the chemical substance being banded because, as described above, the output of this process is an inhalation concentration range and does not directly consider dermal exposure. However, NIOSH is currently evaluating the evidence that may support a separate dermal banding process that would consider the NIOSH skin notation process.

Table 3-24. Criteria for skin corrosion/irritation endpoint.

NIOSH banding criteria for skin corrosion/irritation			
Endpoint Band A	**Endpoint Band B**	**Endpoint Band C**	**Endpoint Band E**
Nonirritating	Mild to moderate irritation	Moderate to severe irritation; reversible direct effects *or* results are mixed or indicate irritant potential with severity unspecified	Skin corrosion; irreversible effects pH value of <2.0 or >11.5

Approach to Data Selection—Skin Corrosion/Irritation

Although skin corrosion and irritation studies are not an obvious choice to support an OEB based on inhalation, NIOSH has determined that data from these studies are useful contributors to the totality of toxicity data for chemical substances. In addition, chemicals that are skin irritants are frequently also respiratory irritants. NIOSH has also evaluated which health endpoints drove the ultimate OEB for 53 chemicals banded by using Tier 2 criteria, as discussed in Chapter 6, and found that the skin irritation/corrosion data drove the final OEB in only 4 cases out of 53. NIOSH has therefore included skin irritation/corrosion data in its banding protocol, although additional research on its utility in the banding process is recommended, as stated in the Future Research Needs section.

For this endpoint, data from authoritative reviews are preferred. Conclusions on skin corrosion and irritation can be based on (1) observational information on humans who are topically exposed to a chemical substance in the workplace or in an emergency situation or (2) experimental data on skin corrosion and irritation or other direct effects on the skin that are associated with a non-immune-mediated mechanism in experimental animals. The following provide information on the potential of a substance to be assigned a band based on the skin corrosion/irritation endpoint:

- Classification system from an authoritative organization (e.g., NIOSH Skin Notation Profiles)
- Conclusions provided by authoritative reviews (e.g., ATSDR, European Chemicals Agency, IRIS, Organisation for Economic Co-operation and Development Screening Information Data Set, REACH assessments)

When various authoritative reviews provide multiple classifications or conclusions, the most stringent band corresponding to those conclusions is selected. The assessment is based on the substance in pure form, unless banding is being developed for a specific product that includes diluted or nonconcentrated material. For example, a strong acid such as hydrochloric acid banded according to this process would be classified as band E for the Skin Corrosion/Irritation endpoint, even though dilute solutions can be nonirritating.

Endpoint-Specific Band Selection—Skin Corrosion/Irritation

NIOSH recommends the following potency criteria for assigning bands for the Skin Corrosion/Irritation endpoint under Tier 2 assessment (Table 3-24), on the basis of classifications provided by authoritative organizations or conclusions provided in authoritative reviews (Table 3-23).

For skin corrosion or irritation, the following guidance is provided:

- Assign band E if the substance is characterized by skin corrosion.
- Assign band C if the substance is characterized as a moderate skin irritant, or if results are mixed or indicate the potential for skin irritation but do not specify severity.
- Assign band B if the substance is characterized as mild or weak irritant.
- Assign band A if the substance is not a skin irritant.
- Other indications that a chemical substance causes irritation include qualitative descriptions that suggest that the chemical substance is associated with erythema, peeling skin, dry or cracked skin, reddening, swelling, and/or itching of the skin. These descriptors can be used to band skin irritants on the basis of the severity of the reaction. Reversible, mild effects that occur at high concentrations should be placed into bands B and C, whereas serious, irreversible effects that occur at low concentrations are banded in band E.

For direct effects on the skin other than skin corrosion/irritation, the following guidance is provided:

- Assign band C if the substance is identified to cause a reversible direct effect on the skin other than irritation/corrosion or if results indicate the potential for a direct effect of the skin associated with a non-immune-mediated mechanism but do not specify severity.

Endpoint Determinant Score—Skin Corrosion/Irritation

If acceptable data on skin corrosion/irritation are available, a score of 5 is assigned as the EDS. The presence of multiple acceptable studies also warrants a score of 5. If there are no available data for skin corrosion/irritation, no band is assigned and the EDS is 0. This score is assigned on the availability of the information, irrespective of the outcome of the test or observation (positive/negative).

3.11 Banding Potentially Hazardous Chemical Substances on the Basis of Eye Damage/Irritation

Serious eye damage is "the production of tissue damage in the eye, or serious physical decay of vision, following application of a test substance to the anterior surface of the eye, which is not fully reversible within 21 days of application." Eye irritation is defined as "the production of changes in the eye following the application of test substance to the anterior surface of the eye, which are fully reversible within 21 days of application" [UNECE 2015].

Data Sources—Eye Damage/Irritation

Sources for Tier 2 information for eye damage/irritation are shown in Table 3-25.

Table 3-25. Information sources for eye damage/irritation endpoint.

Endpoint	Rank	Source of information	Acronym
Eye Irritation	1	Organization for Economic Cooperation and Development	OECD
		World Health Organization International Programme on Chemical Safety	WHO-IPCS
		European Chemicals Agency; Registration, Evaluation, Authorisation, and Restriction of Chemicals	REACH
	2	Agency for Toxic Substances and Disease Registry	ATSDR
		U.S. EPA Integrated Risk Information System	IRIS

Classification Criteria—Eye Damage/Irritation

For a Tier 2 assessment, data for assigning a band to a substance on the basis of its capacity to cause serious eye damage or irritation are typically gathered and evaluated from authoritative reviews conducted by governmental, national, international, and professional agencies with interests in the human health impacts of hazardous chemical substances (Table 3-25). However, for a Tier 2 assessment, NIOSH has not recommended band assignments based on potency information (e.g., dose-response data, Draize scores, etc.) for the eye damage/irritation endpoint. Instead, NIOSH recommends assigning bands on the basis of qualitative data provided by authoritative reviews, as shown in Table 3-26.

Table 3-26. Criteria for eye damage/irritation endpoint.

NIOSH banding criteria for serious eye damage/irritation			
Endpoint Band A	**Endpoint Band B**	**Endpoint Band C**	**Endpoint Band E**
Nonirritating	Mild to moderate irritation	Severe irritation; moderate to severe irritation *OR* Irritant with unspecified severity, no conclusion, or mixed results	Irreversible eye damage

Approach to Data Selection—Eye Damage/Irritation

NIOSH has determined that data from eye damage and irritation studies are useful as indicators of potential respiratory irritation. Eye irritation frequently correlates with respiratory irritation among airborne workplace chemicals. In addition, NIOSH evaluated which health endpoint drove the ultimate OEB for 53 chemicals banded by using Tier 2 criteria, as discussed in Chapter 6, and found that the eye damage/irritation data drove the final OEB in only 3 cases out of 53. NIOSH

has therefore included eye irritation/damage data in its banding protocol, although additional research on its utility in the banding process is recommended, as stated in the Future Research Needs section.

Data provided in authoritative reviews can be used to reach conclusions on eye damage and irritation based on (1) observational information in humans who are splashed in the eye with a chemical substance or exposed to its vapor in the workplace or in an emergency situation and/or (2) experimental data on eye corrosion or irritation in experimental animals. The following provides information on the potential of a substance to be assigned a band based on the eye damage/irritation endpoint:

- Conclusions provided in authoritative reviews from sources listed in Table 3-26 are useful.
- When multiple classifications by various authoritative reviews are available, the most stringent band corresponding to the classifications is selected (Table 3-26).

Endpoint Specific Band Selection—Eye Damage/Irritation

- Assign band E if the chemical substance is characterized as causing irreversible eye damage.
- Assign band C if the chemical substance is characterized as a severe eye irritant or moderate to severe eye irritant, or if results are mixed.
- Assign band B if the chemical substance is characterized as a mild to moderate eye irritant.
- Assign band A if the chemical substance is not an eye irritant.

Endpoint Determinant Score—Eye Damage/Irritation

If acceptable data on eye damage/irritation are available, a score of 5 is assigned as the EDS. The presence of multiple acceptable studies also warrants a score of 5. If there are no available data for eye damage/irritation, no band is assigned and the EDS is 0. This score is assigned on the availability of the information, irrespective of the outcome of the test or observation (positive/negative).

3.12 Uncertainty and the Endpoint Determinant Score

The TDS is an index or measure of data sufficiency for banding and addresses a range of toxicological endpoints that are identified for a particular chemical substance but not the number of studies within each toxicological endpoint. The EDS for each health endpoint indicates the presence or absence of a minimum amount of data to support occupational exposure banding for a particular health endpoint. It does not provide a measure of the robustness of the database for that endpoint. The differing scores for each endpoint (30 for cancer studies, 5 for lethality data) reflect how much weight is given in the banding process for that type of data, not how reliable that endpoint is overall or the importance of that data. In addition, a chemical substance with 16 valid LD_{50} values will receive the same EDS of 5 as a chemical substance with only one valid LD_{50} value. There is likely greater uncertainty in the lethality value of the chemical substance with only one LD_{50} compared with the chemical substance with 16 LD_{50}s. This uncertainty is not addressed in the NIOSH occupational exposure banding process. However, users may want to consider this factor when banding chemical substances. NIOSH has not developed specific guidance on this point.

3.13 Using Human Data for Occupational Exposure Banding

This section addresses the use of qualitative and quantitative human data in band selection at the Tier 2 level. When adequate human data are available, they are typically preferred for occupational exposure banding; the exception is for acute toxicity, which is based on LD_{50}/LC_{50} (in experimental animals only). However, it is important to understand that health effects data in environmentally or occupationally exposed human cohorts frequently are associated with large uncertainties because of the inherent nature of human study design. For example, epidemiological studies often have significant imprecision in quantifying exposures, the duration of exposure, and the likelihood of concurrent exposure to other chemical substances. These issues can all be controlled in experiments with laboratory animals, which reduces uncertainty in those factors but does not address the significant uncertainty inherent in using animal data to predict human response. It is a trade-off. Sometimes the data from human studies are sufficient to provide a clear dose-response with relatively few issues, and in those cases, human data are preferred. In practice, however, few well-documented human exposure data sets are available for dose-response analysis that would be appropriate to support band selection.

Conversely, for endpoints where a categorical outcome can be evaluated on a qualitative or semi-quantitative basis, information on such endpoints as skin and eye irritation and skin and respiratory sensitization may be available from exposed groups or through testing in volunteers. Data describing the presence of an effect or the severity of the outcome—such as no effect, mild, or severe—may contribute to our understanding of the possible effects of the chemical substance on these endpoints. Therefore, human data, when available, may be more easily used for endpoints that use categorical or qualitative data. The following paragraphs give some simple rules for using quantitative and qualitative human exposure information for banding at the Tier 2 level.

Quantitative Information

Human data may be applicable for hazard banding in Tier 2 if all the following criteria apply:

1. The data have been obtained from Rank 1 sources.
2. The Rank 1 authoritative organizations have used them to develop toxicity benchmarks, such as an RfC (US EPA) or MRL (ATSDR).
3. A dose-response relationship is evident from the study used to set the toxicity benchmark, with a clearly defined NOAEL, BMDL, or LOAEL.

Example in which human exposure data are applicable

- The US EPA's RfC for a 2,4- and 2,6-toluene diisocyanate mixture is based on a NOAEL of 0.006 mg/m^3 (0.0009 ppm) that was observed in a prospective occupational cohort study with a decline in lung function as the primary effect [Diem et al. 1982]. This would be a STOT-RE endpoint. A LOAEL of 0.014 mg/m^3 (0.0019 ppm) was given in the summary. Using the LOAEL of 0.0019 ppm and dividing by 10 to adjust to a NOAEL-equivalent gives 0.00019 ppm. According to the NIOSH criteria for STOT-RE, the endpoint band would be **band E**, and an EDS of 30 would apply to these findings.

An example in which animal data better define the primary effect, though supported by human data

- The primary effect of chronic exposure to n-hexane is peripheral neuropathy. This effect has been described in a number of reports on health effects of shoe and leather-goods

workers [Carlomagno et al. 1983; Cavalleri and Cosi 1978; Rizzuto et al. 1977]. However, because these reports contain imprecise information on exposure levels, the US EPA's IRIS database developed an RfC for this compound on the basis of nervous system deficits in Wistar rats, the BMCL of 430 mg/m^3 (122 ppm). Nervous system effects are a STOT-RE endpoint. The endpoint band for n-hexane would be **band D** for this chemical substance. Analyzing the epidemiological studies and reports in the IRIS toxicological review of n-hexane suggests a point-of-departure value (equivalent to a NOAEL or BMDL) for neurotoxicity of approximately 50 ppm. If the chemical substance was banded on the basis of this neurotoxicity information, the STOT-RE endpoint band based on neurotoxicity would also be **band D**. However, the human studies and IRIS toxicological reviews would not be used as the primary source for banding, because they were not used to develop the RfC.

Qualitative Information

Information on categorical outcomes such as skin and eye irritation and skin and respiratory sensitization may be obtained from human studies on the basis of summary statements found in secondary sources such as the WHO-IPCS and OECD and ECHA documents.

3.14 Consideration of Special Categories of Aerosols

The occupational exposure banding process for particles depends on toxicity assumptions that are generally based on information on aerosols in the range of 0.1 to 100 micrometers aerodynamic diameter (microscale particles). Smaller particles are called nanoparticles (defined as particles having at least one dimension of the primary particles <100 nanometers, i.e., <0.1 micrometer) [BSI 2007; ISO 2007, 2008; NIOSH 2009a; ISO 2014]. Nanoscale particles can also form larger agglomerates. As for any chemical substance, the toxicity profile for microscale particles is a function of the dose received at the affected target site (e.g., different regions of the respiratory tract in which inhaled particles deposit or other systemic targets following uptake into the blood). For airborne particles, the amount (e.g., total mass or surface area of the aerosol) that deposited and is retained in the respiratory tract has been associated with the extent and severity of effects in animals and humans [Green et al. 2007; Kuempel et al. 2009; Kuempel et al. 2014]. A dose-response relationship is observed when the incidence or severity of an effect becomes more probable or pronounced with increasing target tissue dose.

Some particles have unique physical characteristics that support modifications to the general occupational exposure banding process. This modification is needed to address the observation that the total mass dose delivered does not always describe well the dose-response behavior for a single chemical substance across all particle sizes and forms. One well-documented example is the respiratory tract toxicity of titanium dioxide (TiO_2), which is associated with the total particle surface area dose retained in the lungs in rodent studies [NIOSH 2011a]. As a result, the NIOSH REL for ultrafine (nanoscale) TiO_2 (0.3 mg/m^3) is lower than the REL for fine (microscale) TiO_2 (2.4 mg/m^3), by the same factor as the relative particle surface area of fine and ultrafine TiO_2 evaluated in the rodent studies [NIOSH 2011a]. Other physical and/or chemical substance properties can also influence the degree of toxicity observed for inhaled particles (e.g., size, shape, surface reactivity, solubility). Examples of other particle categories include liquid aerosols, fibers, and nanoparticle [BSI 2007; ISO 2007, 2008, 2014; NIOSH 2009a]. Recomendations for the application of the occupational exposure banding process for particles in these categories are described in this section.

Liquid aerosols. Particles in the liquid phase can be evaluated by using the NIOSH occupational exposure banding process, regardless of aerodynamic diameter. The toxicity of liquid aerosols is typically driven by the interaction of molecules that reach cellular targets after the material has dissolved or thoroughly dispersed in biological fluids. Such molecular interactions are not expected to vary greatly among exposures to different particle-size distributions of liquid materials (assuming equivalent molecular concentrations among liquid particle sizes). However, differences in the nature and severity of effects could still be observed to the extent that differences in particle sizes result in differences in deposited doses in the respiratory tract regions [Hinds 1982].

Fibers. Microscale fibers are typically defined as having an aspect ratio (length to width) equal to or greater than 3:1 and a length of greater than 5 μm, as measured by phase contrast microscopy [NIOSH 2011b]. Nanofibers have been defined as nano-objects with two external dimensions in the nanoscale and the third dimension that is significantly larger (typically by more than 3 times); the largest external dimension is not necessarily in the nanoscale [ISO 2016]. Other high-aspect-ratio particles include tubes, belts, and whiskers, which can be nanoscale or microscale. Fibers and other high-aspect-ratio particles have unique aerodynamic features that are dependent on their geometry (dimensions) and that influence their deposition in the respiratory tract [Hinds 1982; Asgharian et al. 2018]. In addition, the physical shape and size of fibers can directly influence toxicological properties and the nature of their interactions with target cells[Hinds 1982]. These complexities require using a Tier 3 assessment for fibers, and the OEB Tier 1 and Tier 2 criteria are not recommended. Some hazard banding frameworks for nanomaterials recommend assigning the most stringent band for bio-persistent, rigid nanofibers [ISO 2016].

Nanoscale solid-phase particles. For the purposes of this document, nanoscale particles are defined as particles having at least one dimension of the primary particles <100 nanometers [NIOSH 2009a]. Substantial evidence indicates that for some poorly soluble particles, nanoscale materials are generally more toxic than the same mass dose of the same material as microscale particles (see review in NIOSH [2011a]). A better predictor of toxicity in those cases was total particle surface area dose retained in the lungs in rodents [NIOSH 2011a]. This difference could reflect increases in the available surface area for biochemical reactivity, increased bioavailability at the cellular level, or other factors. In addition, the deposition efficiency of nano-diameter particles in the respiratory tract is greater than that of micro-diameter particles, and a higher proportion of the airborne nano-diameter particles is capable of depositing in the pulmonary (gas-exchange) region of the lungs [Maynard and Kuempel 2005; Oberdörster et al. 2005].

These empirical data and mechanistic hypotheses have been used to support application of the hazard banding procedures within control banding schemes for engineered nanoparticles (e.g., as applied in various national standards [ANSES 2010; ISO 2014]). Using the same rationale, NIOSH recommends that the occupational exposure banding process—when applied to nanoparticles—be modified as follows.

- ***Poorly-soluble nanoscale particles***
  If the toxicity data include NOAELs that were developed specifically for the nanoscale form of the chemical substance, then the NIOSH occupational exposure banding process can be used with no modifications.

- If data are available for only the microscale form of the chemical substance, then the band assignment should be shifted to the next more stringent band, on the assumption that poorly soluble nanoscale substances will likely be more toxic that their microscale equivalents (e.g., by an order of magnitude) [NIOSH 2011a]. Some other banding

schemes (e.g., ISO [2014]) also recommend a more stringent band (to reduce exposure by an order of magnitude) when data are available on only the microscale form of the substance.

- ***Soluble nanoscale particles***
  Data support an association between increased total particle surface area and increased toxicity for poorly soluble nanoscale particles. Because the retained surface area decreases over time for soluble particles (because of dissolution), increased solubility would tend to decrease the potency of particles when the adverse effects are due to the retained particle surface dose. On the other hand, higher solubility could result in increased potency (compared with poorly soluble particles) if the toxic effects are due to released ions or direct interaction of the chemical substance within cells. Thus, as particle solubility increases, there may be less need for the OEB to account for enhanced toxicity due to the nanoparticle-specific characteristics. In the French agency for food, environmental, and occupational health and safety [ANSES 2010] and International Standards Organization [ISO 2014] control banding schemes, soluble particles (defined as solubility in water >0.1 g/L) are addressed with regard to the toxicity of the solute, without consideration of nanoparticle-specific toxicity.

However, given the uncertainties in the relationship of solubility to particle toxicity, NIOSH recommends that in the absence of data to the contrary, all nanoscale particles should be treated in the same manner without regard to solubility. Accordingly, NIOSH recommends shifting the banding assignment to the next more stringent band if data are available only for the microscale form of the agent.

Nanoscale fibers and tubes

Because the toxicity of nanoscale fibers and nanoscale tubes may differ substantially from other forms of the compound, the occupational exposure banding process described in this document may not fully and accurately capture the toxicity of these chemical substances. Therefore, Tier 1 and Tier 2 should not be used. Instead, a Tier 3 assessment is required as described for other fibers.

NIOSH is currently evaluating the state of the science for deriving OELs and OEBs for nanomaterials [NIOSH 2014] and is also examining the process and data for developing hazard categories for nanomaterials based on biological mode of action and physical-chemical properties.

Chapter 4

Tier 3 Occupational Exposure Banding—Using Expert Judgment to Evaluate Experimental Data

The overall concept of the NIOSH occupational exposure banding process is the employment of simple procedures and clear rules for assigning chemical substances to human health–related exposure bands. In Tier 1, this assignment is based on information abstracted from GHS. In Tier 2, it is based on data summarized in authoritative secondary sources such as agency reviews. However, the process recognizes that some chemical substances may not be amenable to these processes because of insufficient information. If a user desires to analyze the potential human health impacts of a chemical substance beyond Tier 2, or when a TDS of 30 cannot be reached, further evaluation may require a detailed survey of the relevant primary literature and analysis of resulting experimental data on the nine primary toxicological endpoints that provide input to the occupational exposure banding process. These procedures should be done by, or in consultation with, persons with experience in evaluating experimental toxicological information. It is important to note that Tier 3 of the occupational exposure banding process is not equivalent to a full quantitative risk assessment based on a systematic review; consequently, there may be differences between a final Tier 3 OEB and an OEL developed through a rigorous risk assessment process.

Important elements of the Tier 3 process include (1) carrying out targeted electronic literature searches of bibliographic databases for research information and data on a chemical substance under consideration, (2) selecting studies of the chemical substance as they apply to the toxicological endpoints under consideration, (3) retrieving copies of appropriate articles from libraries or vendors, and (4) critically reading and evaluating the studies to discern the quality of the study and the toxicological outcomes, including any available dose-response information. Dose-response information may provide a basis for deriving toxicity benchmarks such as NOAELs, LOAELs, SFs, and IURs. Derivation of one or more of these parameters is likely to be critical in assigning chemical substances under evaluation to their most appropriate bands. To this end, the same outcome-specific technical criteria and determinant scores that apply to Tier 2 are used in Tier 3 for band selection and ensuring data sufficiency. This process is shown in Figure 9.

4.1 Tier 3 Procedures

Searching the Literature

It is recommended that a readily available gateway such as PubMed (http://www.ncbi.nlm.nih.gov/pubmed) be used to identify and access the relevant scientific information. Simple search statements linking the chemical substance or its CAS number to the appropriate toxicological and human health outcomes should be constructed. The search should cover the period from

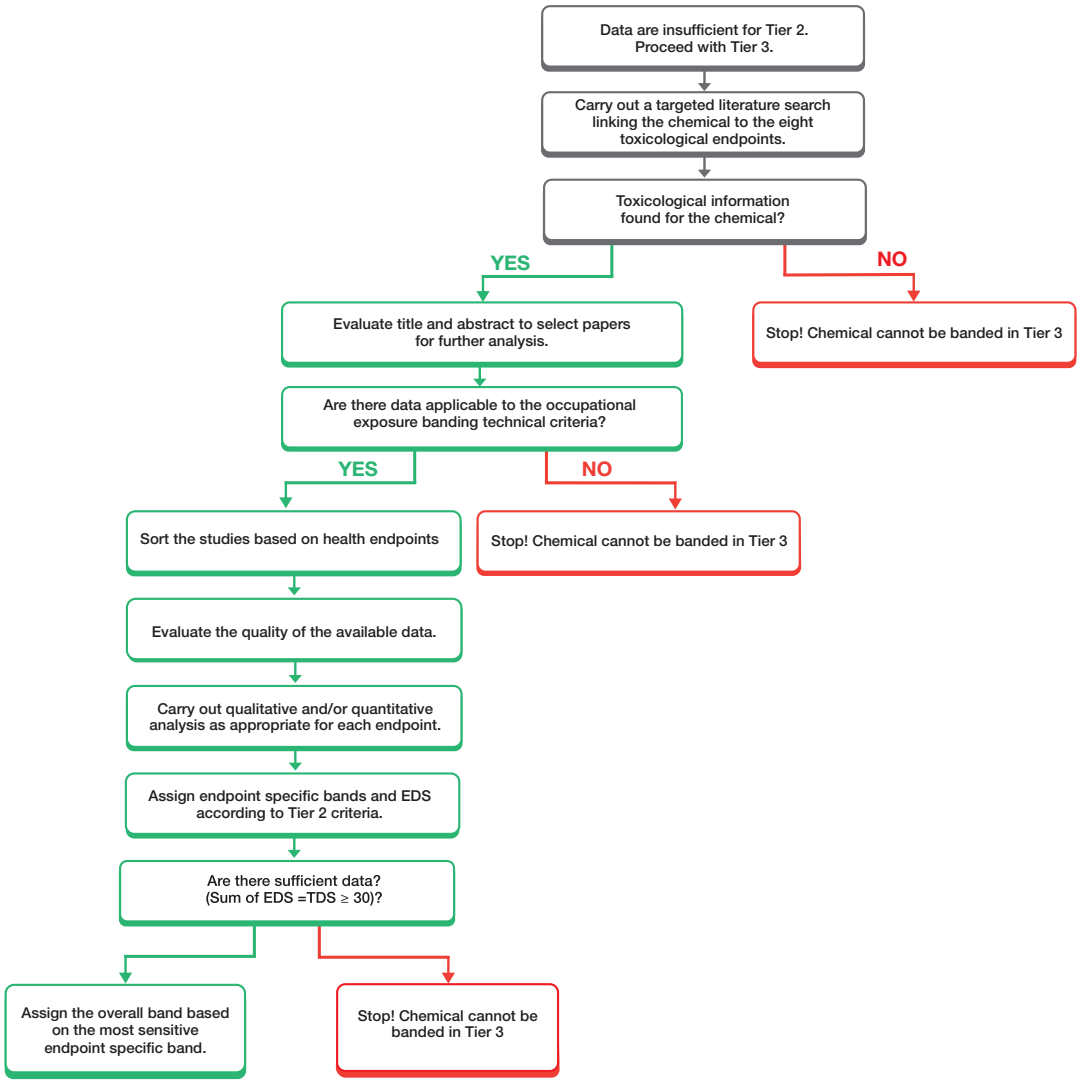

Figure 4-1. Flow chart for the Tier 3 occupational exposure banding process.

the year before the most recently published authoritative review to the present, or it should cover an unlimited period if there are no agency-sponsored documents covering the subject chemical substance.

Selecting Relevant Studies

Titles and abstracts of all "hits" should be reviewed to evaluate whether any of the identified articles are likely to contain categorical and/or dose-response information on the toxicological or human health impacts of the chemical substance under investigation. All potentially relevant articles should be retrieved from libraries or purchased from vendors.

Evaluating the Studies

Expert judgment should be used while reading the studies to determine whether dose-response information on the appropriate toxicological outcomes is available. The primary toxicity benchmark for banding is the NOAEL, then other appropriate benchmarks such as the LOAEL, BMDL, BMCL, or, for cancer incidence data, the SF or IUR may need to be derived. It is assumed that individuals carrying out the Tier 3 evaluation will be knowledgeable of these procedures. Factors to consider include power, standard procedures, model, and limitations. In addition, evaluating the reliability of the toxicological data by using procedures such as the Klimisch score should be considered.

The assessment should use a method to differentiate study quality or reliability. For example, Klimisch and colleagues [Klimisch et al. 1997] proposed such a method by the development of what is now called "Klimisch scores."

- Studies that were carried out according to generally valid and/or internationally accepted testing guidelines (e.g., good laboratory practice) or in which the test parameters documented are based on a specific testing guideline (e.g., OECD testing guideline) are given a Klimisch score of 1. A study with a Klimisch score of 1 is considered "reliable without restriction." Most such studies are conducted by contract laboratories for industry.

- Studies in which the test parameters documented do not totally comply with the specific testing guideline, but are sufficient to accept, are given a Klimisch score of 2. These are studies that were probably not performed under good laboratory practice conditions and did not follow an internationally verified testing guideline (e.g., OECD), but which are nevertheless well documented and scientifically acceptable. Most of these studies are conducted by academia and are considered "reliable with restriction."

- According to Klimisch et al. [1997],

  > "…studies or data from the literature/reports in which there are interferences between the measuring system and the test substance or in which organisms/test systems were used which are not relevant in relation to the exposure (e.g., un-physiologic pathways of application) or which were carried out or generated according to a method which is not acceptable, the documentation of which is not sufficient for an assessment and which is not convincing for an expert judgment…"

  are given a Klimisch score of 3 and are considered "not reliable."

- Studies or data from the literature that do not give sufficient experimental details and that are only listed in short abstracts or secondary literature (e.g., books and reviews) are given a Klimisch score of 4 and are considered "not assignable."

Selecting a Band

Derived toxicity benchmarks such as the NOAEL and any others mentioned above, where applicable, should be compared to the relevant Tier 2 technical criteria for each toxicological endpoint. As before, the most stringent band within and among endpoints should be selected as the overall band.

Judging Data Sufficiency

The availability of information for the toxicological endpoints of interest provides critical input on data sufficiency, in a similar manner to that described for Tier 2. The availability of data on a particular endpoint (for example, reproductive/developmental toxicity) contributes to an EDS which, when combined with those available for other endpoints, should meet or exceed the TDS threshold of 30 out of a possible 125 (if all endpoints were represented). Failure to achieve a TDS of 30 would suggest that the chemical substance cannot be banded in Tier 3 and thus is beyond the scope of the NIOSH occupational exposure banding process.

Assessing Uncertainty

In a similar manner to the Tier 2 evaluation, the TDS addresses the range of toxicological endpoints that are identified for a particular compound but not the number of studies within each toxicological category. Given the higher degree of certainty potentially associated with multiple studies of each endpoint, it is likely that varying degrees of certainty on band selection will be determined for chemical substances where the TDS is above the threshold for sufficiency. Users should be aware that certainty can also be reduced when study results don't agree. Incorporating procedures such as the Klimisch scores may help address this issue.

Chapter 5

Special Issues in Occupational Exposure Banding

5.1 Impacts of Physical Form on OEB Selection

OEBs and Associated Inhalation Exposure Concentration Ranges

After compiling the hazard data for each endpoint, the appropriate overall OEB for the chemical substance is determined by considering all endpoints together. Each of the bands is associated with a range of air concentrations that serves as potential exposure control targets or as an exposure concentration range. Note that the concentration ranges are provided for additional context for the bands to support their application in risk management decision-making. The ranges reflect likely values for a health-based OEL, given a similar health hazard. However, the inhalation exposure concentration ranges are designed only as potential exposure control ranges. Although it is most health-protective to keep exposures below the lower bound of the OEB, the actual control target could reflect any value in the range or other values based on other risk management considerations. These considerations include the level of confidence in the data set, the margin of safety associated with the specific exposure scenario being assessed, and the consequences of selecting an exposure control target that leads to control strategies that are either insufficient or more than necessary.

Selecting the Inhalation Exposure Concentration Range Category

Based on the physical form of the chemical substance, separate inhalation exposure concentration ranges are associated with each band, one for dusts/particles and one for gases/vapors. Guidelines for selecting the inhalation exposure concentration range category are as follows:

- The inhalation exposure concentration ranges for chemical substances that are present in the form of gases or liquids that can form vapors in the occupational environment are provided in units of parts per million.
- The inhalation exposure concentration ranges for bands for exposures to chemical substances that are present in the form of dust/particles are provided in units of mg/m^3 to be consistent with the overall banding criteria (Table 1-1). Individual endpoint criteria may require different units.
- Some chemical substances that are liquids at standard temperature and pressure have sufficiently low vapor pressures that occupational exposure can occur in both the particle phase (as liquid aerosols) and vapor phase. Such chemical substances should generally be compared to the inhalation exposure concentration range category for gas/vapor phase exposures (see details in the section below).

- The inhalation exposure concentration ranges for each band are specific to each physical form and were evaluated against health-based OELs for chemical substances of similar physical characteristics; thus, gas- or vapor-phase chemical substances **should not be converted** to units of mg/m^3 for inhalation exposure concentration range selection. Rather, the OEB is determined first, and the related inhalation exposure concentration range corresponding to that band is provided in the NIOSH occupational exposure banding process.
- If a chemical substance has **two forms** (vapor or particle), the occupational exposure banding process should be completed for both forms, and separate OEBs should be assigned for both forms. Accordingly, the derived occupational exposure band(s) should inform the control strategy for each form of the chemical substance.

Inhalation Exposure Concentration Ranges Differ by Physical Form

The values of the OEB inhalation exposure concentration ranges were developed on the basis of experience with hazard banding processes and evaluation against current OELs. The need for different inhalation exposure concentration ranges by physical form is based on the observation that the distribution of OELs for gases and vapors is shifted to higher concentrations than for dusts and particles when both forms are represented in units of mg/m^3. For example, a relatively low-potency chemical substance vapor such as acetone has a NIOSH REL of 250 ppm (590 mg/m^3). In the context of controlling exposure to particle exposures, a concentration of 590 mg/m^3 is well above the allowable limit for even inert dusts or solid particles, which often have OELs in the range of 1 to 10 mg/m^3. Note that the concentration distributions do overlap, and thus clearly some vapors are more potent than some dusts/particles on an mg/m^3 basis. To avoid the confusion in the differences by physical form, the occupational exposure banding process uses ppm as the preferred concentration units for gases/vapors. For dust or solid particles, the bands are based on mg/m^3.

Certain respiratory tract physiological mechanisms might explain this difference in relative potency distributions on an mg/m^3 basis for gases and vapors versus particles [EPA 1994; Oberdörster 1995, 1988].

- An upper bound limit on exposures to solid particles relates to physical mechanisms in the lung for overloading of normal particle clearance. This particle overload phenomenon caps the potency distribution for dusts/particles but is not relevant for gases and vapors.
- Many toxic chemical substances exert their effects at the level of the tissue response on the basis of local tissue dose. For a given total mass of a chemical substance inhaled, the larger the surface area contacted, the lower the tissue concentration of the chemical substance at any single tissue location. Thus, for soluble dusts/particles, the local tissue dose can be higher for a given total exposure because of high deposition site doses than for gases and vapors that are governed by dose diffusion.
- For insoluble dusts/particles, overall respiratory tract retention time is often higher than for gases and vapors. To the degree that such dusts/particles induce a toxic response, the cumulative dose (reflecting local dose and amount of time the tissue is exposed) can be higher for solid dusts/particles compared to gases and vapors.
- The biological activity of low vapor pressure liquids is complex because such chemical substances have properties that are intermediate between gases and solid dusts/particles. On the basis of analysis of health-based OELs for such low vapor pressure liquids, the OEB inhalation exposure concentration ranges identified using the NIOSH occupational exposure

banding process generally align best with the vapor phase. This might reflect that such liquids dissolve in fluid layers of the respiratory tract and generally act more like vapors than solid dusts/particles in terms of clearance and local tissue doses. Further evaluation could be performed through a Tier 3 assessment when such a case arises.

5.2 Mixed Exposures

Introduction

Workers across all industries are commonly exposed to combinations of chemical substances. However, knowledge is limited about potential health effects from mixed exposures to chemical substances. Research has shown that physiological interactions from some mixed exposures can lead to an increase in severity of the harmful effect. For example, exposure to both carbon monoxide and methylene chloride produces elevated levels of carboxyhemoglobin, reducing the blood's ability to carry oxygen in our bodies. Managing and evaluating mixed exposures are complex issues, given the large number of combinations that occur every day.

History

Risk management strategies for mixed exposures have been unique and depend on the exposures involved, state of the science, the policies employed at the time, and potential health effects. In the first decade of the National Occupational Research Agenda, its Mixed Exposures Team was established to facilitate the study of occupational mixed exposures. In December 2004, the Mixed Exposures Team published a report based on its examination of the literature and ongoing research [NIOSH 2004]. The report is a useful roadmap for understanding the complexity of dealing with mixed exposures. It identified the issues involved and research needed to appropriately handle occupational exposures to mixtures.

Development of OEBs for Mixed Exposures

Few mixed-exposure OELs have been established, because assessment methods for mixed exposures have been based on extrapolation rather than direct toxicological data [Mumtaz et al. 1995]. The current challenge for environmental and occupational scientists is to provide a sound, scientific basis that enables policymakers to substitute current, simplistic, single-chemical standard setting with real-life, mixture-oriented standard setting [Feron et al. 1995].

Given the complexity of mixed exposures, multiple processes are needed to sample and assess exposure and risk. The current state of knowledge does not provide a basis for proposing a single process for risk assessment of mixed exposures. Several methodologies may be considered, including the following:

- Whole-Mixture Process (Mixture Treated as a Single Toxic Agent) [NIOSH 2004]

  Whole-mixture testing considers the mixture as a single entity and conducts a standard health risk assessment for the chemical substance mixture in the same way that one is conducted for a single chemical substance. It is the simplest way to study the effects of a mixture, because the sole information needed to apply this process is the dose-response curve of the whole mixture in the organism desired.

- Similar-Mixture Process [NIOSH 2004]

  The similar-mixture process uses data on a well-studied but toxicologically similar mixture to estimate the risk from the mixture. Mixtures are usually judged to be toxicologically similar on the basis of composition or observed toxicological properties.

- Group of Similar Mixtures Process [NIOSH 2004]

  In the similar-mixtures process or comparative-potency method approach, the human toxicity of the mixture is estimated from that mixture's toxicity in a nonhuman study by multiplying by a proportionality constant that is estimated from data on the other mixtures.

- Component-Based Mixture Processes [NIOSH 2004]

  A single component of a chemical substance mixture may be a relevant index of toxicity when that component is suspected to account, qualitatively and quantitatively, for most of the toxicity. This process is useful, under the appropriate conditions, because only the dose-response information for the indicator is required. This method should be used only when synergy is not expected or known.

Banding Mixtures of Chemical Substances

Employees may also be exposed to chemical substances that cannot be separated in production, chemical substances that have been intentionally blended into a mixture, natural chemical substances comprising numerous individual chemical substances, and individual chemical substances from various sources in their workplaces. In these situations, special considerations should be given on the basis of whether health-effect literature for the mixture is available. If such information is not available for a chemical mixture, the OEBs should be derived independently for each chemical constituent. These bands will be considered chemical substance by chemical substance in this mixed exposure and will guide the risk management decisions. Care should be taken to determine whether the mixed exposure has any synergistic effects.

Chapter 6

Preliminary Evaluation of Tier 1 and Tier 2 Banding Processes

Consistency and usability of the NIOSH occupational exposure banding process with OELs are both important to the success of the banding process. To evaluate the occupational exposure banding decision logic, NIOSH addressed the following questions:

- Do the Tier 1 and Tier 2 banding processes produce an exposure range (band) at least as health protective as the most stringent OEL developed by other processes?
- Which health endpoints are most influential as the basis of OEBs?
- Are Tier 1 OEBs at least as stringent as the Tier 2 bands?
- Does the Tier 2 banding process produce consistent and specific endpoint bands when applied by different users?

For the purpose of this evaluation, NIOSH compared Tier 1 and Tier 2 OEBs to existing OELs for chemical substances. This is not an equal comparison, given several considerations. OEBs are completely health-based concentration ranges based on the totality of the toxicity information available for a specific chemical substance. OELs, by contrast, are derived with additional considerations, including possible adjustments for analytical feasibility, engineering control achievability, and in some cases economic factors. Consequently, given these additional adjustments for OELs, the OEBs and OELs will not always align perfectly.

The following sections outline the Tier 1 and Tier 2 analysis conducted by NIOSH to evaluate the consistency and usability of the NIOSH occupational exposure banding process with OELs.

6.1 Evaluation of Tier 1 Criteria

Although NIOSH does not recommend banding of chemical substances when authoritative OELs are available, OELs are used in this Tier 1 evaluation as indicators of health hazard and potency. To evaluate the Tier 1 process, NIOSH asked the following question: **Does the Tier 1 banding process produce an exposure range (band) at least as health protective as the most stringent OEL developed by other processes?** In the evaluation, NIOSH compared the OELs of 804 chemical substances to the NIOSH-determined Tier 1 OEBs for the same chemical substances. As stated earlier, OELs are not a perfect standard for comparison; however, they represent the current exposure level to which chemical hazards should be controlled. The chemical substances selected for this exercise have been assigned at least one full-shift OEL from the following: NIOSH RELs, OSHA PELs, and Cal/OSHA PELs, German maximum workplace concentrations (MAKs), ACGIH® TLVs®, or AIHA WEELs.

NIOSH evaluated whether the determined inhalation exposure concentration range associated with an OEB encompassed the most stringent OEL value available from the selected OEL sources for each of the 804 chemical substances. The criterion for acceptance of the Tier 1 process was that the assigned OEB would either contain the OEL or be more health-protective than the OEL for at least 80% of the chemical substances. Eighty percent was used as the acceptable criterion rather than a lower percentage because NIOSH determined it was the minimum level providing sufficient confidence in the Tier 1 process. A higher percentage was not selected because it might diminish the usefulness of the banding process by making the Tier 1 OEBs even more health-protective than the current criteria. If the Tier 1 banding process was at least as health-protective as the OEL for at least 80% of the chemical substances, then this would demonstrate support for using the GHS codes and categories to assign OEBs.

When more than one OEL was available for a chemical substance, the lowest OEL was used for comparison. This step would further diminish bias that might be inherent to OELs based on the date the OEL was established and the agency of origin. Table 6-1 shows the number of times an agency's OEL was used for the comparisons. Note that the sum of sources in Table 6-1 is greater than 804 because for nearly half of the comparisons, two or more of the agencies had the minimum OEL. The minimum OEL came from two sources 118 times, three sources 134 times, four sources 92 times, and five sources 37 times.

Table 6-1. Sources of OELs for the Tier 1 evaluation exercise.

Source of Minimum OEL	Frequency
TLV®	448
MAK	204
WEEL	106
NIOSH REL	324
CAL/OSHA PEL	356
OSHA PEL	176

The sum is greater than 804 because the minimum OEL came from two or more sources 381 times.

NIOSH retrieved GHS H-codes and categories from the GESTIS database for 606 of the 804 chemical substances. These data on 606 chemical substances were used for the NIOSH Tier 1 comparison. NIOSH compared the OELs for 414 gas/vapor chemical substances and 192 dust/particle chemical substances with their bands derived from the Tier 1 criteria based on GHS H-codes and categories.

In Figures 6-1 and 6-2, the OEL (x-axis) is compared to the Tier 1 band (y-axis). Each circle represents an individual chemical substance. The colors of the areas within the figure represent the levels of protection that the OEB offers, compared to the OEL value; the protection offered by the OEB is based on the inhalation exposure concentration ranges provided in Table 1-1. For gases/vapors (Figure 6-1), 91% of the chemical substances (376/414) were assigned a band in Tier 1 that was at least as health-protective as the OEL band used for comparison (shown in

green), which exceeded the criterion of acceptance of 80%. It is important to note that on the basis of the NIOSH criteria, chemical substances cannot be assigned to band A or B in Tier 1, so any chemical substance with lower toxicity would be assigned to band C. For 32 of the 414 chemical substances (8%), the Tier 1 OEB was one band less health-protective (shown in yellow), and for 6 of the 414 chemical substances (1%), the Tier 1 OEB was two bands less health-protective (shown in red).

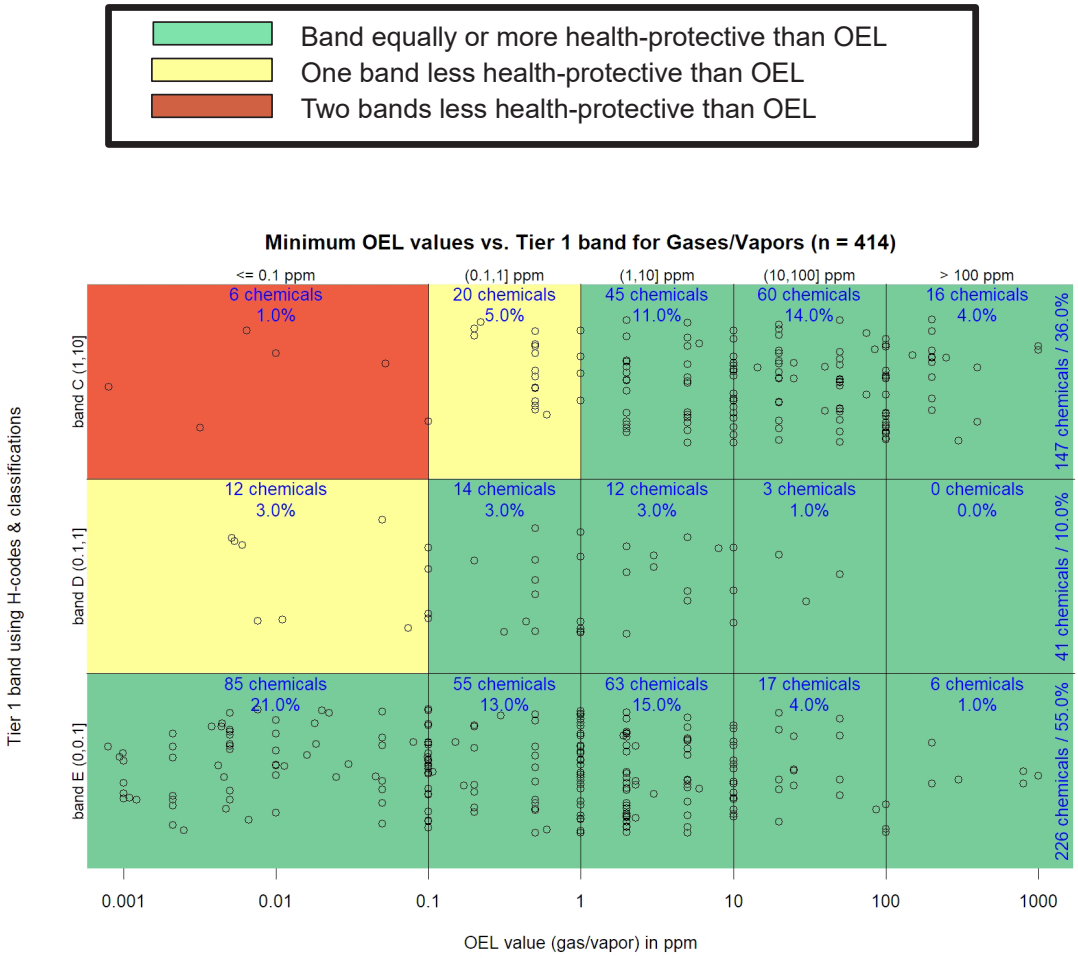

Figure 6-1. Minimum OEL values vs. Tier 1 band for gases/vapors.

For dusts/particles (Figure 6-2), 93% of the chemical substances (179/192) banded in Tier 1 were assigned a band that was at least as health-protective as the OEL band used for comparison (shown in green), which met the initial criterion of acceptance of 80%. As stated above, on the basis of the NIOSH criteria, chemical substances cannot be assigned to band A or B in Tier 1, so any chemical substance with lower toxicity would be assigned to band C. For 10 of the 192 chemical substances (5%), the band was one band less health-protective (shown in yellow), and for 3 of the 192 chemical substances (2%), the Tier 1 OEB was two bands less health-protective than the OEL band (shown in red).

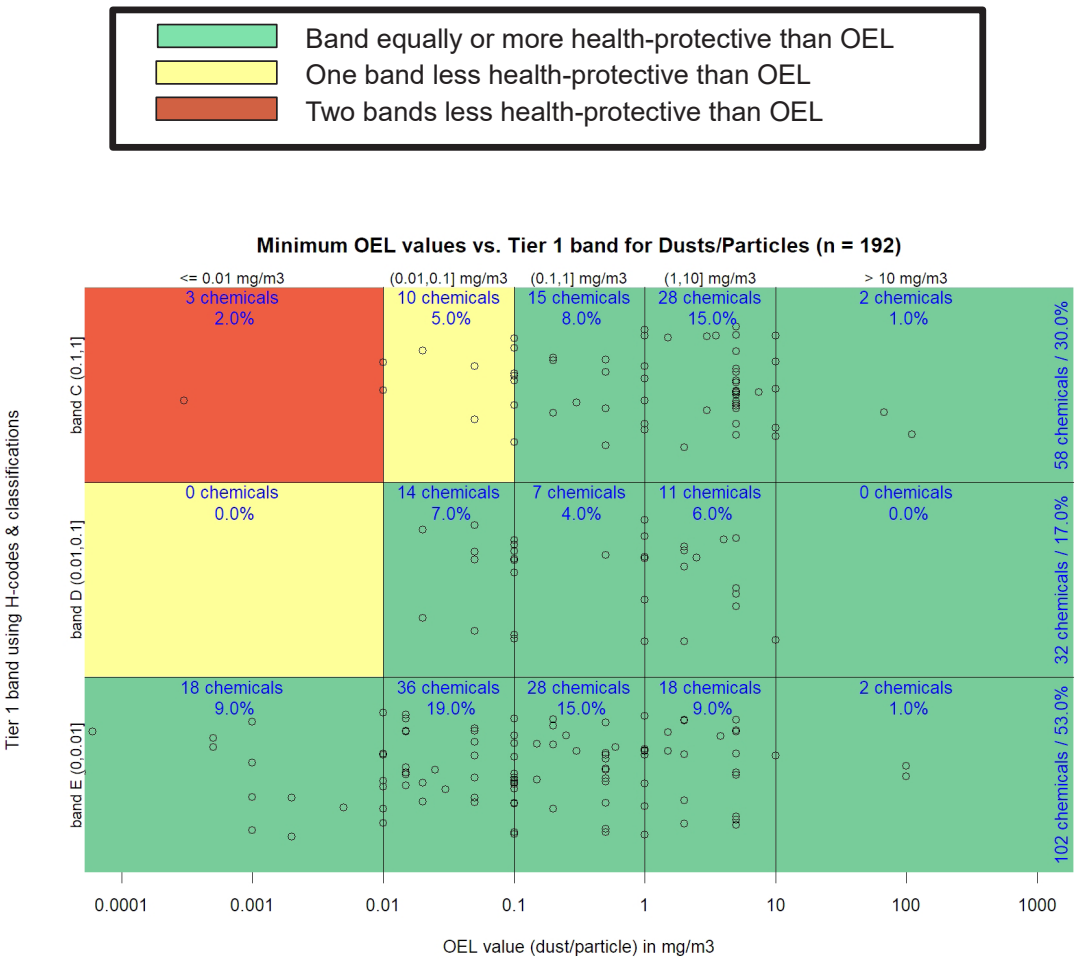

Figure 6-2. Minimal OEL values vs. Tier 1 band for dusts/particles.

The overall agreement between the derived Tier 1 OEBs and OELs exceeded the NIOSH a priori criterion for acceptance. This exercise provided confidence that chemical substances banded by using only GHS H-codes and categories in the Tier 1 process would be appropriately classified according to their potential to cause adverse health effects. However, the process did not band chemical substances with 100% consistency. Because OELs and GHS H-codes and categories were typically developed at different times and possibly based on different information, the correspondence between banding based on GHS H-codes and categories and OELs is not perfect. This may be due to variability in how the OELs were set, the policy decisions made during the development of the OEL, or new information reflected in the GHS H-codes and categories that was not available when the OEL was developed.

Upon determining that the Tier 1 banding process produces an exposure range (band) at least as health protective as the most stringent OEL developed by other processes, NIOSH sought to answer the following question: **Which health-effect endpoints were most influential as the basis of Tier 1 OEBs?** The 606 chemicals described above were analyzed to understand which endpoints drove the final Tier 1 OEB. NIOSH determined that for 66% of the chemical substances

(401/606), the overall Tier 1 OEB was based on an acute endpoint (respiratory and skin sensitization, acute toxicity, genotoxicity, skin corrosion/irritation, or eye damage/irritation). For 34% of the chemical substances (205/606), the overall Tier 1 OEB was based on a chronic endpoint (cancer, reproductive toxicity, or STOT-RE). In a subset of 11% of the chemical substances (65/606) for which the band was based on a chronic endpoint, an acute endpoint also indicated the same band, so in effect, the Tier 1 OEB was based on both a chronic and acute endpoint. (Note: If both acute and chronic endpoints were identified as the most stringent band, then the basis was attributed to the chronic endpoint for purposes of this exercise.)

NIOSH banding criteria are designed to give more weight to the presence of data for chronic health endpoints than acute health endpoints, so this may indicate that GHS H-codes may not adequately capture the totality of the toxicity information available. Therefore, NIOSH strongly recommends that users take advantage of the increased information available in Tier 2 to increase the reliability of the banding; it also recommends that the Tier 2 process be completed for all chemical substances when the user has sufficient expertise and adequate data are available.

6.2 Evaluation of Tier 2 Criteria

As stated previously, although NIOSH does not recommend banding chemical substances when authoritative OELs are available, OELs are used in this Tier 2 evaluation as indicators of health hazard and potency. NIOSH sought to answer the following questions:

- **Does the Tier 2 banding process produce an exposure range (band) at least as health protective as the most stringent OEL developed by other processes?**
- **Are Tier 1 Bands at least as stringent as the Tier 2 Bands?**
- **Which health endpoints are most influential as the basis of OEBs?**
- **Does the banding process produce consistent and specific endpoint bands when applied by different users?**

Comparison of Tier 2 Bands with OELs

This analysis sought to answer the following question: **Does the Tier 2 banding process produce an exposure range (band) at least as health protective as the most stringent OEL developed by other processes?** Accordingly, OELs of 53 chemical substances were compared to the Tier 2 OEBs for the same chemical substances. The 53 chemical substances used in this analysis were randomly chosen from a variety of databases such that they had an OEL and were determined preliminarily to have sufficient endpoint-specific data for Tier 2 analysis. NIOSH selected the chemical substances from these databases: the EPA IRIS database, the TLV® List, the MAK list, and the Health Canada Health-Based Tolerable Daily Intakes chemical substance list. This analysis was done similarly to the Tier 1 evaluation, where users banded 53 chemical substances in the Tier 2 process and the resulting bands were compared with the minimum OEL for each of these chemicals. Although OELs are not a perfect standard for comparison, they represent the current recommended exposure control targets. As in the Tier 1 comparison with OELs, the NIOSH target was to have the Tier 2 band be at least as health-protective as the OEL, at least 80% of the time.

In Figure 6-3 the exposure range corresponding to the band containing the OEL is displayed on the x-axis and is compared to the Tier 2 band on the y-axis. Of the 53 chemical substances

selected, Tier 2 banding was completed for 46. The seven chemical substances that could not be banded in Tier 2 because of insufficient data (TDS <30) had minimum OELs that fell in the range corresponding to:

- Band B (n = 3)
- Band C (n = 3)
- Band D (n = 1)

Of the 46 chemical substances banded, the Tier 2 band was at least as health-protective as the OEL band used for comparison (shown in green) for 45 chemical substances (98%). Although this may suggest that the bands could be more health protective than initially intended, this is considered acceptable because of the small sample size (n = 45) and for consistency with Tier 1 criteria. For 1 of 46 chemical substances (2%), the Tier 2 band was two bands less health-protective than the OEL (shown in red). Of the 46 chemicals banded, the OELs for 14 chemicals (30%) fell within the exposure range corresponding to the OEB. For 16 chemicals (35%), the OEB was one band more stringent than the OEL. And for 15 chemicals (33%), the OEB was two or more bands more stringent than the OEL.

Ideally, all of the OELs would be found in the exposure range corresponding to the OEB. In the case of the chemical substances analyzed here, however, the Tier 2 banding was somewhat more stringent than the corresponding OEL. Reasons for this include that the OEBs are based solely on health data, whereas OELs often include factors such as analytical feasibility, availability of engineering controls, and economic considerations. In addition, OELs have been set in different time periods and may have been based on different data than are currently available for occupational exposure banding.

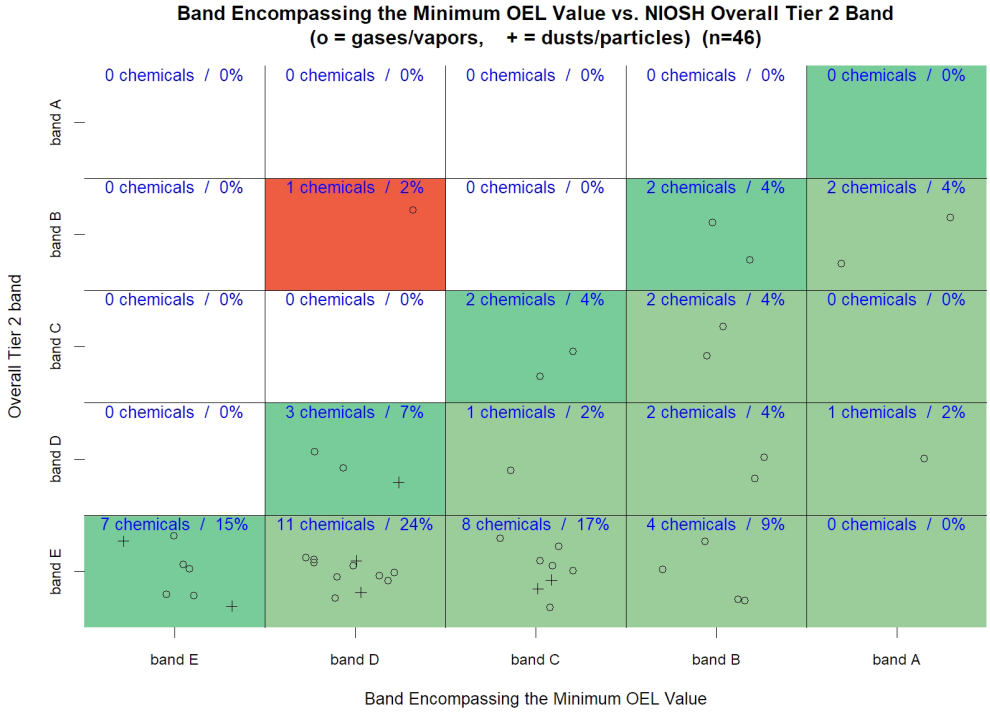

Figure 6-3. Comparison of minimum OEL and Tier 2 bands.

Comparison of Tier 1 and Tier 2 Banding Results

Next, NIOSH compared results from the Tier 1 and Tier 2 banding processes for the same chemical substances, to answer the question of whether the **Tier 1 bands were at least as stringent as Tier 2 bands for most chemical substances.** NIOSH used the Tier 2 process to band a subset of 53 of the 804 chemical substances banded with the Tier 1 process. The target for acceptability was that the Tier 1 band would be at least as stringent as the Tier 2 band for 80% of the chemical substances. Forty one of the 53 chemical substances had sufficient information to be banded in both Tier 1 and Tier 2. Of the 12 chemical substances that could not be banded in Tier 1 and Tier 2,

- one could not be banded in either Tier 1 or Tier 2
- six were banded in Tier 1 but did not have sufficient information to band them in Tier 2
- five did not meet the criteria for banding in Tier 1 but had sufficient information to band them in Tier 2.

The comparisons of the Tier 1 and Tier 2 banding processes for the 41 remaining chemical substances with both Tier 1 and Tier 2 OEBs are provided in Figure 6-4. For 63% of the chemical substances (26/41), the Tier 1 and Tier 2 processes produced the same bands. For 17% of chemical substances (7/41), the Tier 1 band was more stringent than the Tier 2 band. For the remaining 20% of chemical substances (8/41), the Tier 2 band was more stringent than the Tier 1 band. The Tier 1 band was at least as stringent as the Tier 2 band for 80% percent of the chemical substances, which met the initial target of 80%.

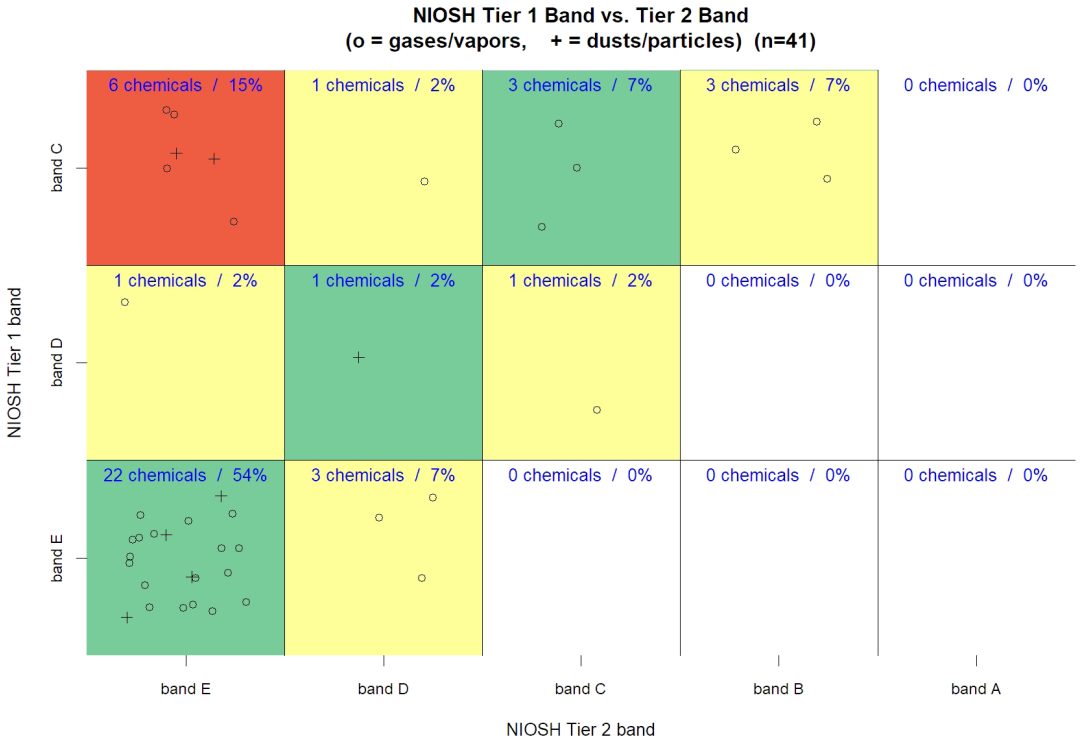

Figure 6-4. Comparison of Tier 1 and Tier 2 bands.

NIOSH also performed an analysis to address the following question: **Which health endpoints are most influential as the basis of OEBs?** To do so, NIOSH examined the health-endpoint basis of these same 41 chemicals used in the Tier 1/Tier 2 comparison above. Although NIOSH had analyzed the health-endpoint bases of Tier 1 OEBs on 606 chemicals (see section 6.1), to ensure comparability it pulled out this subset of 41 chemicals to compare directly the endpoint bases of the Tier 1 and Tier 2 bands.

NIOSH found that the health endpoints driving Tier 1 bands were mostly acute (23/41, or 56%) (respiratory and skin sensitization, acute toxicity, genotoxicity, skin corrosion/irritation, or eye damage/irritation), as found in the larger sample of 606 chemicals (where the percentage driven by acute endpoints was 66%), with 44% (18/41) driven by chronic health endpoints. A subset of the 18 bands driven by the chronic endpoints (6/41, or 15%) was driven by both a chronic and acute health endpoint (see Table 6-2).

Conversely, the health endpoints that drove the overall Tier 2 OEBs were primarily chronic (cancer, reproductive toxicity, or STOT-RE). For this sample of chemicals, the Tier 2 OEB was based on chronic endpoints 78% of the time (32/41 chemicals). Only 22% of the time (9/41) was an acute health endpoint identified as the sole basis of the OEB. However, as in the analysis of the larger 606 chemical data set in section 6.1, a subset of chemicals (29%) had both a chronic and acute health endpoint identified as a potential basis for the OEB (see Table 6-2). (Note: If both acute and chronic endpoints were identified as the most stringent band, then the basis was attributed to the chronic endpoint for the purposes of this exercise.)

Table 6-2. Endpoint Category contributing to the overall band for Tier 1 and Tier 2 (n = 41).

Endpoints	Tier 1	Tier 2
Chronic	44%	78%
Acute	56%	22%

This analysis shows that the distributions of the health endpoint bases for Tier 1 and Tier 2 were different, with Tier 1 banding primarily driven by acute endpoints and Tier 2 primarily driven by chronic endpoints for the same chemicals. The reasons for this difference likely include that Tier 1 makes use of only GHS H-codes and categories, whereas Tier 2 makes use of an array of quantitative and qualitative data more reflective of the overall toxicity of the chemical. The Tier 2 process significantly weights the chronic health endpoints, which is consistent with the development of 8-hour time-weighted average inhalation concentration ranges. Overall, this analysis provides additional support for the NIOSH recommendation to proceed to Tier 2 banding for all chemicals, to better reflect their overall toxicity.

Evaluation of Tier 2 Criteria–Consistency

For this analysis, NIOSH sought to answer this question: **Does the occupational exposure banding process produce consistent endpoint bands when applied by different users?**

The Tier 2 criteria were evaluated for precision and usability by comparing the results across different users. A total of 43 occupational hygienists or persons who had knowledge of occupational hygiene principles were recruited to evaluate the process.

Each user received 4 hours of training from NIOSH researchers involved in development of the banding processes. The amount of time required to teach and demonstrate the Tier 1 process to users was relatively short. Substantially more time was necessary to train users effectively on Tier 2. Each user received the same two chemical substances (chemical substance 1 and chemical substance 2), blank data sheets, and a copy of the draft occupational exposure banding document. The two chemical substances were chosen because they did not have an existing OEL and it was predetermined that users would be able to find relevant data for most endpoints. Reviewers emailed their results to NIOSH, and they were compiled anonymously. Of the recruited users, 18 completed the full process and submitted banding information.

Tier 1 results were identical for all users for both chemical substances. Tier 2 results showed that the overall band was consistent among users. However, individual endpoint–specific bands showed less consistency when the criteria were qualitative in nature. For chemical substance 1, 12 of 17 users obtained an overall Tier 2 band D. One user banded this chemical substance in band C, one in band E, and two in band B. One user did not band this chemical substance, and another did not find sufficient data to band the chemical substance. For chemical substance 2, 12 of 18 users obtained an overall Tier 2 band E, and six users obtained band D.

The acute toxicity endpoint had the most agreement among users who banded both chemical substances: 13 of 17 users of banding chemical substance 1 and 14 of 18 users banding chemical substance 2 assigned identical bands for the acute toxicity endpoint, as shown in Table 6-3 and Table 6-4, respectively. The band assigned for other health endpoints showed less consistency. For example, reproductive toxicity showed the least consistency, with responses ranging from band A to band E for chemical substance 1 and from band A to band C for chemical substance 2. There were also several endpoints, such as respiratory sensitization, that for both chemical substances the majority of users found no data to band.

The TDS (measure of presence of data for each endpoint) varied across users. For chemical substance 1, the scores ranged from 25 (<30, therefore insufficient to band) to 105, with a mean of 84 and median of 90. For chemical substance 2, scores ranged from 40 to 125, with a mean of 83 and median of 90. Results are presented in detail in Figure 6-5 and Figure 6-6.

Table 6-3. Tier 2 occupational exposure banding agreement by endpoint for chemical substance 1, among 17 users.

Chemical Substance 1										
Band	Cancer	Repro	STOT-RE	Genotox	Resp sen	Skin sen	Acute	Skin irr	Eye irr	Overall band
A	1	5	–	9	2	9	13	1	2	–
B	–	2	14	–	–	–	–	4	4	2
C	1	4	2	5	–	–	–	1	–	1
D	12	1	–	–	–	–	–	–	–	12
E	–	1	–	–	–	–	–	–	–	1
No band	3	4	1	3	15	8	4	11	11	1
No. of users	17	17	17	17	17	17	17	17	17	17

Abbreviations: sen = Sensitization, irr = Irritation, STOT-RE = Specific Target Organ Toxicity-Repeated Exposure

Table 6-4. Tier 2 occupational exposure banding agreement by endpoint for chemical substance 2, among 18 users.

	Chemical Substance 2									
Band	Cancer	Repro	STOT-RE	Genotox	Resp sen	Skin sen	Acute	Skin irr	Eye irr	Overall band
A	–	1	–	1	2	2	–	–	–	–
B	–	6	1	–	–	–	14	7	4	–
C	–	4	9	10	–	–	–	5	6	–
D	8	–	3	–	–	–	–	–	–	6
E	9	–-	1	7	–	–	–	–	–	12
No band	1	7	4	–	16	16	4	6	8	–
No. of users	18	18	18	18	18	18	18	18	18	18

Abbreviations: sen = Sensitization, irr = Irritation, STOT-RE = Specific target organ toxicity-repeated exposure

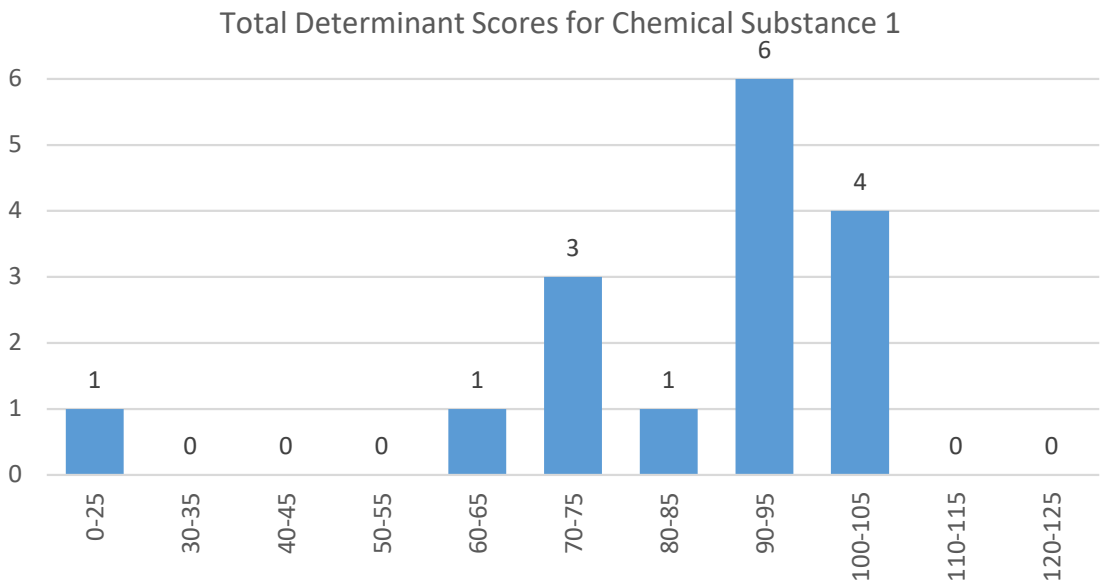

Figure 6-5. Distribution of total determinant scores for chemical substance 1.

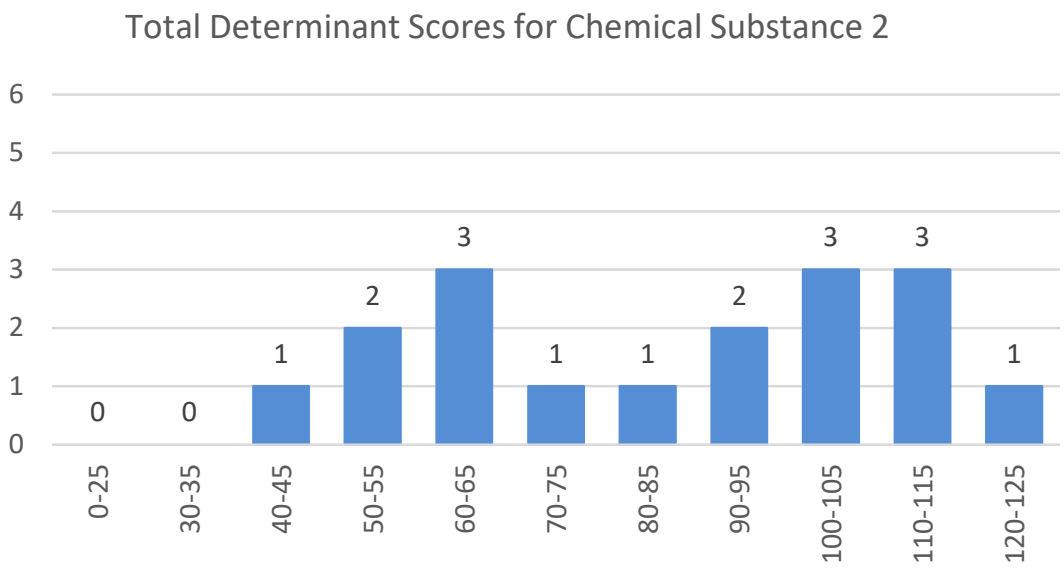

Figure 6-6. Distribution of total determinant scores for chemical substance 2.

NIOSH compared the results of the Tier 1 and Tier 2 process for these two chemical substances. For chemical substance 1, the overall Tier 1 band and the overall Tier 2 band most users obtained were identical: band D. However, for chemical substance 2, the overall Tier 1 band was C, whereas most users obtained band E as the overall Tier 2 band.

Closer examination of the data for chemical substance 2 indicates that the overall Tier 2 band was driven by the cancer and genotoxicity endpoints, whereas the overall Tier 1 band was driven by acute toxicity, skin irritation, and eye irritation. This was due to the fact that the H-codes for cancer (H350 and H351) and genotoxicity (H340 and H341) were not present in the GESTIS Substance Database or other relevant sources. This resulted in an overall Tier 1 band C. For Tier 2, however, all but one user located information on cancer for this chemical substance, with a majority of users banding the chemical substance in band E. This reinforces the NIOSH recommendation to complete the Tier 2 banding process whenever possible. Relying on a Tier 1 band is not recommended, because the H-codes may not be complete or as up-to-date as information found in the recommended data sources for Tier 2.

Discussion of Tier 2 Evaluation

Since 2014, NIOSH has conducted a number of exercises to evaluate consistency and usability among users of the banding process as well as to refine the descriptions of the process in this document. A detailed analysis of the individual evaluations was described above, and Tables 6-3 and 6-4 summarize the evaluation activities, primarily focusing on Tier 2.

Key points can be identified in the analyses of the evaluation phases, as shown in Table 6-5. Other salient factors that will be critical to OEB dissemination activities in the future have also been highlighted. Users of Tier 2 should fully understand how to use the NIOSH process. Discrepancies between users in selecting endpoint bands seem to be related to ability to locate data, which was determined by analyzing what sources each user used to find the relevant data to band the chemical substance. In response, NIOSH has clarified the instructions to ameliorate this issue.

Table 6-5. Summary of evaluation activities for Tier 2.

Evaluation Title	Phase 1 Evaluation	Phase 2 Evaluation	Phase 3 Evaluation	Phase 4 Evaluation	Phase 5 Evaluation
Time frame	May 2014	Sep 2014	Jun 2015	Sep 2015	Oct 2016
Purpose	To prototype training and conduct preliminary interrater reliability	To conduct large-scale banding effort and refine process	To review endpoint results with interrater reliability	To obtain additional data on Tier 2 endpoints to determine level of detail within endpoint descriptions	To assess consistency and usability of the banding process for additional chemical substances
NIOSH training class completed	Yes	Yes	Yes	Yes	Yes
Number of chemical substances	10	102	3	3	20
Number of chemical substances with OELs	10	53	0	0	20
Number of reviewers	9	10	43	18	4
Tier 1 evaluated	Yes	No	Yes	Yes	Yes
Tier 2 evaluated	Yes	Yes	Yes	Yes	Yes
Lessons learned from evaluation	Some data source websites linked to another, of lesser quality	Some endpoints such as skin sensitization needed more information	Reviewer recruitment was easy, but it was difficult to obtain completed information from users; learning curve was significant	Confusion on TDS scoring in some cases	Good agreement with endpoints based upon quantitative data

(Continued)

Table 6-5 (Continued). Summary of evaluation activities for Tier 2.

Evaluation Title	Phase 1 Evaluation	Phase 2 Evaluation	Phase 3 Evaluation	Phase 4 Evaluation	Phase 5 Evaluation
Time frame	May 2014	Sep 2014	Jun 2015	Sep 2015	Oct 2016
How was banding process or document refined?	Data sources curtailed to ensure data quality	Materials with key sources created; skin sensitization end-point documentation rewritten	Genotoxicity endpoint description rewritten; training on Tier 2 rede-signed with example	TDS streamlined and enhanced for clarity	Endpoints based on qualitative data such as genotoxicity further refined to aid in finding information sources

The Tier 2 criteria generally operated as expected, and the resulting bands showed overall consistency among users. Completing a Tier 2 evaluation requires substantial effort not unlike other decision logic frameworks in the occupational hygiene toolbox. Reviewers reported that banding a single chemical substance required hours to days to complete. But this amount of time and effort is substantially less than what is required for a full quantitative risk assessment used to establish an OEL. The variability in TDS scores reflects that users found different subsets of the available data, indicating differing levels of effort or expertise in navigating the sites. This may be less important for actual users, who are highly motivated to evaluate their chemical substances of interest.

For some endpoints, substantial variability was noted in the endpoint-specific band among users. The variability in some endpoints appeared to be related to the clarity of the instructions and the ease of using the criteria. It is important that users read the occupational exposure banding guidance document in its entirety before attempting to band chemical substances. Compliance with this recommendation has been somewhat difficult to attain. The users often consulted training slides rather than the full instructions, to more quickly use the banding process. Key details explained in the document were often missed by only using the training slides, which contributed to variability in the banding results. This points to a need for a more streamlined and reproducible process. Given these observations, the guidance document was streamlined to enhance the consistency and usability of the banding process. In addition, an online e-Tool is available to facilitate the occupational exposure banding process. After each evaluation phase, enhancements were made to the occupational exposure banding document, e-Tool, and training materials, thereby improving the process.

Chapter 7

Future Research Needs

NIOSH has dedicated significant resources and efforts to develop, assess, and validate the occupational exposure banding strategy. The strategy and e-Tool have been subjected to multiple rounds of testing to determine reliability and evaluate potential sources of error. Even so, NIOSH recognizes the need for ongoing assessment of the usability and underlying science of the occupational exposure banding strategy and accompanying e-Tool. Among the research needs that NIOSH recognizes and anticipates with its broader use and increased familiarity for intended audiences are the issues described below.

- The recommended data sources identified for use in the Tier 2 process to assess the nine health endpoints may need periodic evaluation and updating. At the time the occupational exposure banding strategy was developed, these were determined to be the most appropriate data sources aligned with each individual health endpoint. However, it is possible that these may evolve as additional toxicological data become available; accordingly, research to re-evaluate and re-align the data sources with the health endpoints may be useful. Allowances for consideration of proprietary data sources may also be warranted for specific health endpoints.

- NIOSH was deliberate in establishing a system of minimum data requirements using the endpoint determinant scores (EDSs) for individual health endpoints and the total determinant score (TDS), to provide users with a simple process to assess data availability and the corresponding confidence to band a chemical substance appropriately. With continued use and testing of the occupational exposure banding strategy, this system of scoring may require updates or adjustments. Currently, the strategy suggests that if one of the health endpoints indicates band E (highest toxicity, lowest exposure range) and the TDS is less than 30 (i.e., below the minimum data requirement), then the user should default to band E. This is designed to recommend the most protective risk-management approach until additional data can suggest otherwise. Research evaluating this approach to assess its utility based on use and feedback would be helpful in refining the recommendations.

- As more users adopt and use the occupational exposure banding process, it will be important to conduct evaluations on the consistency and usability of the banding process. Although NIOSH has thoroughly evaluated the banding process, as shown in Chapter 6, it will be important to periodically evaluate the banding process with a larger sample size to ensure that the updated banding process works as intended.

- The occupational exposure banding strategy is based on an 8-hour time-weighted average (TWA) approach for risk management of work exposure. Future research may be helpful to determine whether the strategy can be adapted for shorter time periods more consistent with short-term exposure limits (STELs) or ceiling limits (C) to address the possibility that chemical substances can have short-term health effects.

- NIOSH recognizes that some individual health endpoints (such as genotoxicity and skin corrosion/irritation) may be less predictive of the overall recommended band for a chemical substance than other health endpoints. Research evaluating the predictive potential of individual health endpoints could provide valuable information to help refine the banding process.
- As a companion effort to development of the occupational exposure banding guidance for airborne exposures, NIOSH may consider occupational exposure banding approaches for dermal effects. This focus is an acknowledgement of the need to protect workers from chemical substances that have direct, systemic, or sensitization effects on the skin.
- Research leading to potential modification or adaptation of the occupational exposure banding strategy to address specifically conditions associated with emergency response scenarios would also be a valuable contribution.
- Further automation of the e-Tool and its data retrieval capabilities would serve to enhance usability and further improve consistency of results.
- To expand the audience of potential users of the occupational exposure banding strategy and e-Tool, the development of training tutorials using various media may be indicated, according to user feedback.

As NIOSH continues to promote the occupational exposure banding strategy and its use increases across audiences of safety and health practitioners, employers, workers, and risk managers, the process and e-Tool can benefit from continuing research efforts to inform decisions on risk management of chemical exposures in the workplace.

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Appendix A

Helpful Information for Banding Chemical Substances in Tier 1

This Appendix provides supplemental information needed to band chemical substances in Tier 1. Figure A-1 gives a brief overview of the Tier 1 banding process. Table A-1 provides the NIOSH Tier 1 banding criteria. Once users gather the H-codes and hazard categories necessary to complete Tier 1, they can then apply these data to the NIOSH criteria to determine an endpoint-specific band. H-codes and categories can be retrieved from the GESTIS substance database, the Annex VI database, or a reliable OSHA-compliant SDS. Table A-2 provides a worksheet that can be filled out to record the Tier 1 process. A web tool is also available to assist with this process: https://www.cdc.gov/niosh/topics/oeb/default.html. Refer to Chapter 1 of this guidance document for more specific details on conducting the Tier 1 banding process.

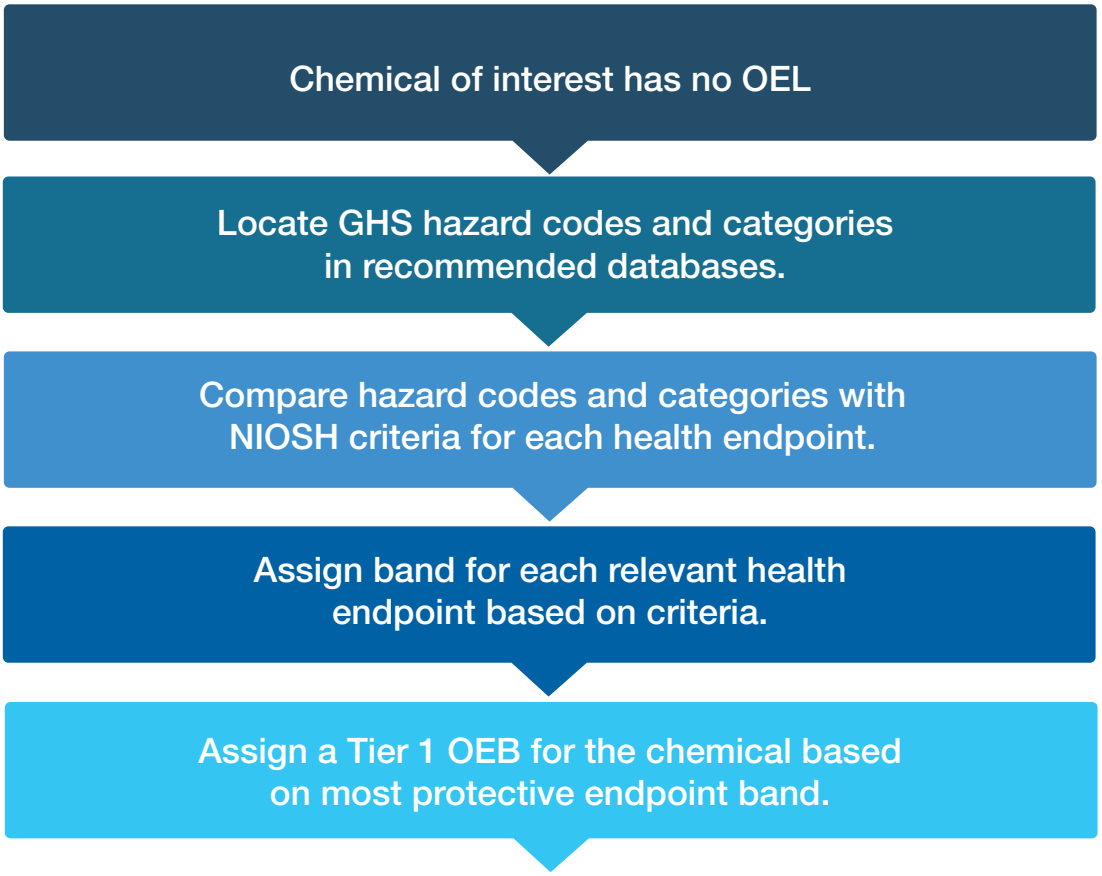

Figure A-1. Steps in the Tier 1 banding process.

Table A-1. Tier 1 criteria overview: GHS H-codes and categories for Tier 1*.

NIOSH Tier 1 Criteria	C	D	E
Exposure ranges			
Dust/particle	>0.1 to ≤1 mg/m^3	>0.01 to ≤0.1 mg/m^3	≤0.01 mg/m^3
Gas/vapor	>1 to ≤10 ppm	>0.1 to ≤1 ppm	≤0.1 ppm
Carcinogenicity	—	—	H350, Category 1, 1A, or 1B
	—	—	H351, Category 2
Reproductive toxicity	H361, Category 2	H360, Category 1B	H360, Category 1 or 1A
Specific target organ toxicity-repeated exposure	H371, Category 2	—	H370, Category 1
	H373, Category 2	—	H372, Category 1
Genotoxicity	—	H341, Category 2	H340, Category 1, 1A or 1B
Respiratory and skin sensitization	H317, Category 1B (skin)	H317, Category 1 or 1A	—
	H335, Category 3	H334, Category 1B	H334, Category 1 or 1A
Acute toxicity	H301, Category 3	H300, Category 2	H300, Category 1
	H302, Category 4	H300, Category 2	H300, Category 1
	H331, Category 3	H330, Category 2	H330, Category 1
	H332, Category 4	H330, Category 2	H330, Category 1
	H311, Category 3	H310, Category 2	H310, Category 1
	H312, Category 4	H310, Category 2	H310, Category 1
Skin corrosion/ irritation	H315, Category 2	—	H314,Category 1, 1A, 1B, or 1C
Eye damage/ irritation	H319, Category 2, 2A or 2B	—	H318, Category 1

*Note that the following H-codes are not used for Tier 1 banding: H200s, H303, H304, H305, H313, H316, H320, H333, H336, H362, and H400s. These H-codes are either not occupationally relevant or not sufficient because they reflect oral hazards or reflect other health endpoints.

Abbreviations: mg/m^3 = milligrams per cubic meter; ppm = parts per million

This blank worksheet can be used to record H-codes, hazard categories, information sources, and the corresponding endpoint-specific band, based on the NIOSH criteria. The most stringent of these bands is recorded at the bottom of the worksheet. This is the Tier 1 OEB for the chemical substance.

Table A-2. Tier 1 worksheet for the banding process.

Chemical Name: **CAS number:**				
Endpoint	**Hazard code**	**Hazard category**	**H-code source**	**Endpoint band**
Carcinogenicity				
Reproductive Toxicity				
Specific Target Organ Toxicity				
Genotoxicity				
Respiratory and skin sensitization				
Acute Toxicity				
Inhalation				
Oral				
Dermal				
Skin corrosion/ irritation				
Eye damage/ irritation				
Most stringent band				

Notes:

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Appendix B

Helpful Information for Banding Chemical Substances in Tier 2

This appendix provides supplemental information on banding chemical substances in Tier 2. Figure B-1 provides a brief overview of the Tier 2 banding process. Table B-1 provides a list of the assigned EDSs for each of the nine toxicological endpoints used in Tier 2 to determine the TDS. Table B-2 provides a list of recommended data sources for each of the nine endpoints. Table B-3 provides a decision tree, data sources, NIOSH criteria, and a blank worksheet for each of nine endpoints, which can be used to band a chemical substance one endpoint at a time. Table B-4 provides a checklist that can be used to highlight the data that have been collected for each specific endpoint. Table B5 provides the complete table of each of the healthy endpoints for banding in Tier 2. A web tool is also available to assist with this process, at https://www.cdc.gov/niosh/topics/oeb/default.html. Refer to Chapter 2 for more specific details on the Tier 2 banding process.

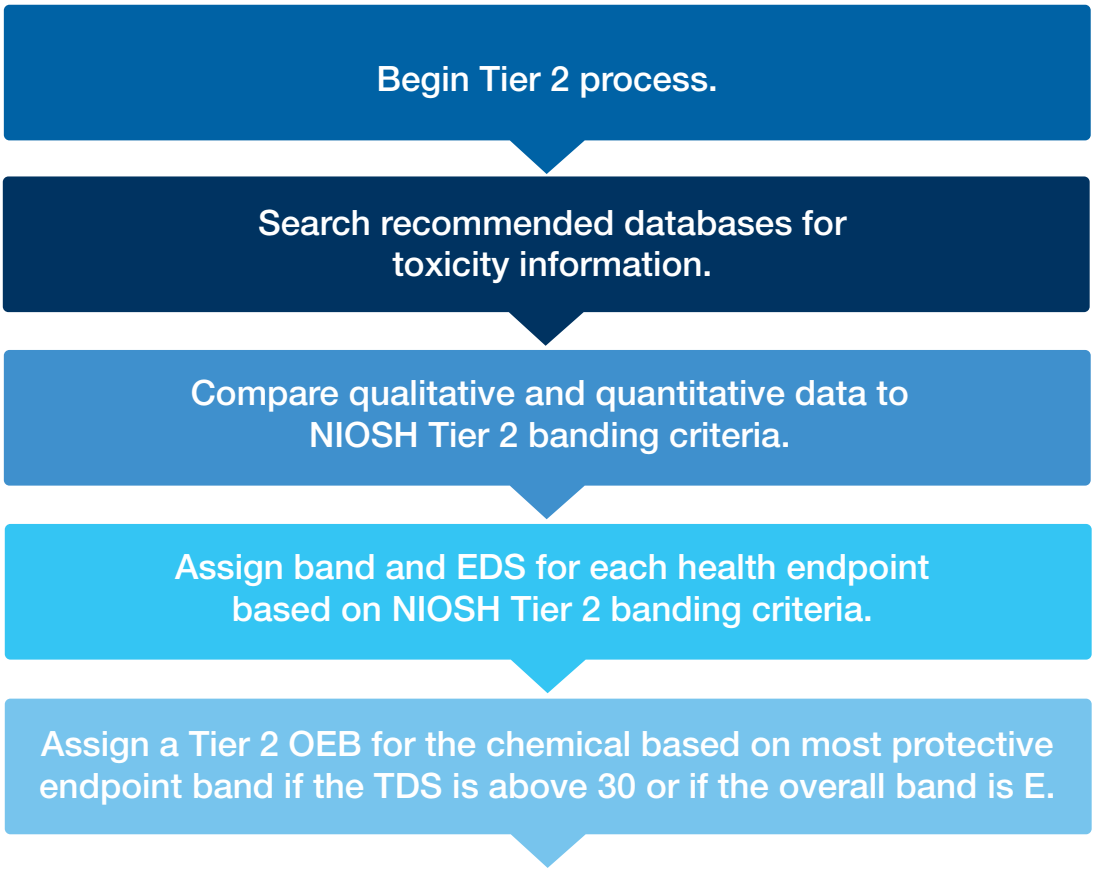

Figure B-1. Overview of the Tier 2 process.

Table B-1. Total determinant score: assigned scores for the presence of toxicological endpoints encountered in the Tier 2 evaluation.

Toxicological endpoint	Endpoint Determinant Score (EDS)
Carcinogenicity	Qualitative (WOE) = 20 or 30 Quantitative = 30
Reproductive and Developmental Toxicity	30
Specific Target Organ Toxicity (STOT-RE)	30
Genotoxicity	5
Respiratory Sensitization	10
Skin Sensitization	5
Acute Toxicity/Lethality (LD_{50} or LC_{50})	5
Skin Corrosion/Irritation	5
Eye Damage/Irritation	5
Data Sufficiency/Total Determinant Score (TDS)*	30/125

The minimum TDS criteria are waived if any of the endpoint bands are E. In that case, the chemical substance is assigned an overall band E, regardless of TDS.

Table B-2. Data sources for banding in Tier 2.

Endpoint	Rank	Source of information*	Acronym
Carcinogenicity	1	US National Toxicology Program Report on Carcinogens [NTP-RoC 2016]	NTP-RoC
		US EPA Integrated Risk Information System [EPA 2014]	IRIS
		International Agency for Research on Cancer [IARC 2015]	IARC
		Health Canada [Health-Canada 1996]	HC
		State of California Office of Environmental Health Hazard Assessment [CAL/EPA 2010]	Cal OEHHA

(Continued)

Table B-2 (Continued). Data sources for banding in Tier 2.

Endpoint	Rank	Source of information*	Acronym
Reproductive Toxicity	1	US National Toxicology Program [NTP 2016]	NTP
		Health Canada [Health-Canada 1996]	HC
		California Environmental Protection Agency [CAL/EPA 2016]	CalEPA
		Agency for Toxic Substances and Disease Registry Toxicological Profiles [ATSDR 2016]	ATSDR
	2	Organization for Economic Co-operation and Development [OECD 2016]	OECD
		World Health Organization International Programme on Chemical Safety [WHO-IPCS 2015]	WHO-IPCS
		US EPA Office of Pesticides: Reregistration Eligibility Decision Documents [EPA 2016a]	EPA RED
		European Chemicals Agency; Registration, Evaluation, Authorisation and Restriction of Chemicals [ECHA 2016]	REACH
Specific Target Organ Toxicity (STOT-RE)	1	Agency for Toxic Substances and Disease Registry Toxicological Profiles [ATSDR 2016]	ATSDR
		US EPA Integrated Risk Information System [EPA 2014]	IRIS
		California Environmental Protection Agency [CAL/EPA 2016]	CalEPA
		US National Toxicology Program [NTP 2016]	NTP
		Health Canada [Health-Canada 1996]	HC
	2	European Chemicals Agency; Registration, Evaluation, Authorisation and Restriction of Chemicals [ECHA 2016]	REACH
		Organization for Economic Co-operation and Development [OECD 2016]	OECD
		World Health Organization International Programme on Chemical Safety [WHO-IPCS 2015]	WHO-IPCS

(Continued)

Table B-2 (Continued). Data sources for banding in Tier 2.

Endpoint	Rank	Source of information*	Acronym
Genotoxicity	1	US National Toxicology Program [NTP 2016]	NTP
		Agency for Toxic Substances and Disease Registry Toxicological Profiles [ATSDR 2016]	ATSDR
		US National Toxicology Program Report on Carcinogens [NTP-RoC 2016]	NTP-RoC
		World Health Organization International Programme on Chemical Safety [WHO-IPCS 2015]	WHO-IPCS
	2	Hazardous Substance Data Bank [HSDB 2016]	HSDB
		European Chemicals Agency: Registration, Evaluation, Authorisation and Restriction of Chemicals [ECHA 2016]	REACH
Respiratory Sensitization	1	Organization for Economic Co-operation and Development [OECD 2016]	OECD
		European Chemicals Agency: Registration, Evaluation, Authorisation and Restriction of Chemicals [ECHA 2016]	REACH
		World Health Organization International Programme on Chemical Safety [WHO-IPCS 2015]	WHO-IPCS
	2	Agency for Toxic Substances and Disease Registry Toxicological Profiles [ATSDR 2016]	ATSDR
		US EPA Integrated Risk Information System [EPA 2014]	IRIS
		Association of Occupational and Environmental Clinics [AOEC 2016]	AOEC
Skin Sensitization	1	NIOSH Skin Notation Profiles [NIOSH 2009]	SK Profiles
		European Chemicals Agency: Registration, Evaluation, Authorisation and Restriction of Chemicals [ECHA 2016]	REACH
		Organization for Economic Co-operation and Development [OECD 2016]	OECD
		World Health Organization International Programme on Chemical Safety [WHO-IPCS 2015]	WHO-IPCS
	2	Hazardous Substance Data Bank [HSDB 2016]	HSDB

(Continued)

Table B-2 (Continued). Data sources for banding in Tier 2.

Endpoint	Rank	Source of information*	Acronym
Acute Toxicity	1	National Library of Medicine ChemID Plus [ChemID 2016]	ChemID Plus
		US EPA Superfund Chemical Data Matrix [EPA 2016b]	EPA SCDM
		Pesticide Properties Database [PPDB 2007]	PPDB
		World Health Organization International Programme on Chemical Safety [WHO-IPCS 2015]	WHO-IPCS
	2	Hazardous Substance Data Bank [HSDB 2016]	HSDB
		Agency for Toxic Substances and Disease Registry Toxicological Profiles [ATSDR 2016]	ATSDR
Skin Corrosion/ Irritation	1	NIOSH Skin Notation Profiles [NIOSH 2009]	SK Profiles
		World Health Organization International Programme on Chemical Safety [WHO-IPCS 2015]	WHO-IPCS
		European Chemicals Agency; Registration, Evaluation, Authorisation and Restriction of Chemicals [ECHA 2016]	REACH
		Organization for Economic Co-operation and Development [OECD 2016]	OECD
		Agency for Toxic Substances and Disease Registry Toxicological Profiles [ATSDR 2016]	ATSDR
		US EPA Integrated Risk Information System [EPA 2014]	IRIS
Eye Damage/ Irritation	1	Organization for Economic Co-operation and Development [OECD 2016]	OECD
		World Health Organization International Programme on Chemical Safety [WHO-IPCS 2015]	WHO-IPCS
		European Chemicals Agency; Registration, Evaluation, Authorisation and Restriction of Chemicals [ECHA 2016]	REACH
	2	Agency for Toxic Substances and Disease Registry Toxicological Profiles [ATSDR 2016]	ATSDR
		US EPA Integrated Risk Information System [EPA 2014]	IRIS

These links are up to date as of December 11, 2017.

Table B-3. Simplified data selection criteria for Tier 2.

Endpoint	Tier 2 data selection criteria
Carcinogenicity	Quantitative ▪ Based on potency information: slope factor, inhalation risk unit, tumorigenic dose (TD_{05}) or concentration (TC_{05})* Qualitative ▪ Based on weight of evidence assessment from authoritative reviews
Reproductive toxicity	Internationally accepted test guideline (e.g., GLP or OECD) studies preferred Based on NOAEL, BMDL, or BMCL* values that assess ▪ Developmental toxicity ▪ Perinatal and postnatal toxicity ▪ One-generation or two-generation toxicity ▪ Reproductive/developmental toxicity ▪ Combined repeated-dose toxicity study with reproductive/ developmental toxicity ▪ Short-term or long-term repeated-dose toxicity (e.g., impairment of reproductive function in the absence of significant generalized toxicity) If no NOAEL or BMDL values are available, use LOAEL, if available, divided by 10 to estimate a NOAEL equivalent.
Specific Target Organ Toxicity (STOT-RE)	Based on authoritative reviews, if available Based on NOAEL or BMDL value from a study of at least 28 days If study duration ≥90 days, reported NOAEL or BMDL is used. If study duration ≥28 days but <90 days, NOAEL is divided by 3 to estimate a 90-day equivalent NOAEL. If no NOAEL or BMDL values are available, use LOAEL, if available, divided by 10 to estimate a NOAEL equivalent. If multiple NOAELs or BMDLs are available for an exposure route, use the lowest route-specific value.
Genotoxicity	Qualitative assessment based on authoritative reviews, when available
Respiratory sensitization	Qualitative assessment based on authoritative reviews, when available

(Continued)

Table B-3 (Continued). Simplified data selection criteria for Tier 2.

Endpoint	Tier 2 data selection criteria
Skin sensitization	Qualitative ▪ Based on human patch testing for sensitization, when available Potential quantitative bases: ▪ LLNA EC3 ▪ GMPT ▪ Buehler guinea pig test
Acute toxicity	Acute lethality data expressed as LD_{50} or LC_{50} Routine experimental animals, e.g., rats, mice, rabbits, guinea pigs Route of administration: oral, dermal, or inhalation. Exclude subcutaneous, intraperitoneal, intravascular routes. Single dose. Exclude multiple-dose studies. For more information on the exclusion criteria for this endpoint, refer to Section 3.9.
Skin corrosion/ irritation	Qualitative assessment from authoritative organizations or authoritative reviews, when available Assessment based on a chemical substance in its pure form unless exposure banding targeted at a specific product with diluted or non-concentrated chemical substance
Eye damage/ irritation	Qualitative assessment based on authoritative reviews, when available

BMCL = Benchmark concentration lower bound; BMDL = benchmark dose lower bound; GLP = good laboratory practices; GPMT = guinea pig maximization test; LC_{50} = lethal concentration 50%; LD_{50} = lethal dose 50%; LLNA EC3 = local lymph node assay effective concentration required to produce a three-fold increase in the stimulation index, compared to vehicle-treated controls; LOAEL = lowest adverse effect level; NOAEL = no observable adverse effect level; OECD = Organisation for Economic Cooperation and Development.

*Associated with a 5% increase in tumor incidence or mortality.

Table B-4. Endpoint-specific criteria for the Tier 2 banding process.

Carcinogenicity data sources

Endpoint	Rank	Source of information	Acronym
Carcinogenicity	1	U.S. National Toxicology Program Report on Carcinogens	NTP-RoC
		U.S. EPA Integrated Risk Information System	IRIS
		International Agency for Research on Cancer	IARC
		Health Canada	HC
		State of California Office of Environmental Health Hazard Assessment	Cal OEHHA

Criteria for carcinogenicity toxicity (quantitative analysis)

NIOSH banding criteria for carcinogenicity			
Exposure/ dosing route	**Band C**	**Band D**	**Band E**
Slope factor	<0.01 (mg/kg-day)−1	≥0.01 to <10 (mg/kg-day)−1	≥10 (mg/kg-day)−1
Inhalation unit risk	<3 × 10−6 (µg/m^3)−1	≥3 × 10−6 to <0.01 (µg/m^3)−1	≥0.01 (µg/m^3)−1
TD_{05}	>5 mg/kg-day	>0.005 to ≤5 mg/kg-day	≤0.005 mg/kg-day
TC_{05}	>16,700 µg/m^3	>5 to ≤16,700 µg/m^3	≤5 µg/m^3

(Continued)

Table B-4 (Continued). Endpoint-specific criteria for the Tier 2 banding process.

Criteria for carcinogenicity toxicity (qualitative analysis)

Classification	Band	Determinant score
National Toxicology Program Report on Carcinogens		
Known to be human carcinogen	E	30
Reasonably anticipated to be human carcinogen	E	30
Environmental Protection Agency Integrated Risk Information System		
Group A (human carcinogen)	E	30
Carcinogenic to humans	E	30
Group B1 (probable human carcinogen)	E	30
Group B2 (probable human carcinogen)	E	30
Likely to be carcinogenic to humans	E	30
Group C (possible human carcinogen)	D	20
Suggestive evidence of carcinogenic potential	D	20
Group D (not classifiable as to human carcinogenicity)	No band	No score
Data are inadequate for an assessment of carcinogenic potential	No band	No score
Group E (evidence of non-carcinogenicity for humans)	A	30
Not likely to be carcinogenic to humans	A	30
International Agency for Research on Cancer		
Group 1 (carcinogenic to humans)	E	30
Group 2A (probably carcinogenic to humans)	E	30
Group 2B (possibly carcinogenic to humans)	E	30
Group 3 (not classifiable as to its carcinogenicity to humans)	No band	No score
Group 4 (probably not carcinogenic to humans)	A	30
State of California Office of Environmental Health Hazard Assessment		
Type of toxicity = cancer	E	30

(Continued)

Table B-4 (Continued). Endpoint-specific criteria for the Tier 2 banding process.

Worksheet for carcinogenicity

Carcinogenicity (0, 20, or 30 points possible)	Band A	Band C	Band D	Band E
NTP/EPA/IARC/Canada/California (QUALITATIVE)				
US EPA IRIS Slope Factor				
US EPA IRIS Inhalation Unit Risk				
Health Canada TD_{05}				
Health Canada TC_{05}				
California Slope Factor				
California Inhalation Unit Risk				

Reproductive toxicity data sources

Endpoint	Rank	Source of information	Acronym
Reproductive Toxicity	1	U.S. National Toxicology Program	NTP
		Health Canada	HC
		California Environmental Protection Agency	CalEPA
		Agency for Toxic Substances and Disease Registry Toxicological Profiles	ATSDR
	2	Organization for Economic Co-operation and Development	OECD
		World Health Organization International Programme on Chemical Safety	WHO-IPCS
		U.S. EPA Office of Pesticides: Reregistration Eligibility Decision Documents	EPA RED
		European Chemicals Agency: Registration, Evaluation, Authorisation, and Restriction of Chemicals	REACH

(Continued)

Table B-4 (Continued). Endpoint-specific criteria for the Tier 2 banding process.

Criteria for reproductive toxicity endpoint

NIOSH banding criteria for reproductive toxicity (NOAEL/BMDL/BMCL)					
Exposure/ Dosing route	**Band A**	**Band B**	**Band C**	**Band D**	**Band E**
Oral, dermal	>300 mg/kg-day	>30 to ≤300 mg/kg-day	>3 to ≤30 mg/kg-day	>0.3 to ≤3 mg/kg-day	≤0.3 mg/kg-day
Inhalation (gases/vapors)	>10,000 ppm	>1,000 to ≤10,000 ppm	>100 to ≤1,000 ppm	>10 to ≤100 ppm	≤10 ppm
Inhalation (dust/particles)	>10,000 $\mu g/m^3$	>1,000 to ≤10,000 $\mu g/m^3$	>100 to ≤1,000 $\mu g/m^3$	>10 to ≤100 $\mu g/m^3$	≤10 $\mu g/m^3$

Worksheet for reproductive toxicity

Reproductive toxicity (0 or 30 points possible)					
Data Supports	**Band A**	**Band B**	**Band C**	**Band D**	**Band E**
If data available, put in this row corresponding to the correct band criteria; otherwise leave blank.					
Source, Rank 1 or 2					

(Continued)

Table B-4 (Continued). Endpoint-specific criteria for the Tier 2 banding process.

Specific Target Organ Toxicity (STOT-RE) data sources

Endpoint	Rank	Source of information	Acronym
Specific Target Organ Toxicity (STOT-RE)	1	Agency for Toxic Substances and Disease Registry Toxicological Profiles	ATSDR
	2	U.S. EPA Integrated Risk Information System	IRIS
		California Environmental Protection Agency	CalEPA
		U.S. National Toxicology Program	NTP
		Health Canada	HC
		European Chemicals Agency: Registration, Evaluation, Authorisation and Restriction of Chemicals	REACH
		Organization for Economic Co-operation and Development	OECD
		World Health Organization International Programme on Chemical Safety	WHO-IPCS

Criteria for Specific Target Organ Toxicity (STOT-RE) Endpoint

NIOSH Banding Criteria for Specific Target Organ Toxicity (NOAEL/BMDL)					
Exposure/ dosing route	**Band A**	**Band B**	**Band C**	**Band D**	**Band E**
Oral, Dermal	>1,000 mg/ kg-day	>100 to ≤1,000 mg/kg-day	>10 to ≤100 mg/kg-day	>1 to ≤10 mg/kg-day	≤1 mg/kg-day
Inhalation (dust/particles)	>30,000 µg/m^3	>3,000 to ≤30,000 µg/m^3	>300 to ≤3,000 µg/m^3	>30 to ≤300 µg/m^3	≤30 µg/m^3
Inhalation (gases/vapors)	>30,000 ppm	>3,000 to ≤30,000 ppm	>300 to ≤3,000 ppm	>30 to ≤300 ppm	≤30 ppm

Multiple NOAELs for one chemical substance may be available. The NOAEL selected for banding should be the NOAEL used by the agency as the basis for the reference dose/concentration.

(Continued)

Table B-4 (Continued). Endpoint-specific criteria for the Tier 2 banding process.

Worksheet for Specific Target Organ Toxicity–Repeated Exposure (STOT-RE) Endpoint

Specific Target Organ Toxicity (STOT-RE) (0 or 30 points possible)					
Data Supports	**Band A**	**Band B**	**Band C**	**Band D**	**Band E**
If data available, put data, notes, etc., in this row corresponding to the correct band criteria; otherwise leave blank.					
Source, Rank 1 or 2					

Genotoxicity Data sources

Endpoint	Rank	Source of information	Acronym
Genotoxicity	1	U.S. National Toxicology Program	NTP
		Agency for Toxic Substances and Disease Registry	ATSDR
		U.S. National Toxicology Program Report on Carcinogens	NTP-RoC
		World Health Organization International Programme on Chemical Safety	WHO-IPCS
	2	Hazardous Substance Data Bank	HSDB
		European Chemicals Agency: Registration, Evaluation, Authorisation, and Restriction of Chemicals	REACH

Criteria for genotoxicity endpoint

NIOSH banding criteria for genotoxicity		
Band A	**Band C**	**Band E**
Negative results	Mixed results	Positive results

(Continued)

Table B-4 (Continued). Endpoint-specific criteria for the Tier 2 banding process.

Worksheet for genotoxicity

Genotoxicity (0 or 5 points possible)			
Data Supports	**Negative results (Band A)**	**Mixed results (Band C)**	**Positive results (Band E)**
If data available, put in this row corresponding to the correct band criteria; otherwise leave blank.			
Source, Rank 1 or 2			

Respiratory sensitization data sources

Endpoint	Rank	Source of information	Acronym
Respiratory Sensitization	1	Organization for Economic Co-operation and Development	OECD
		European Chemicals Agency: Registration, Evaluation, Authorisation and Restriction of Chemicals	REACH
		World Health Organization International Programme on Chemical Safety	WHO-IPCS
	2	Agency for Toxic Substances and Disease Registry	ATSDR
		U.S. EPA Integrated Risk Information System	IRIS
		Association of Occupational and Environmental Clinics	AOEC

Criteria for respiratory sensitization endpoint

NIOSH banding criteria for respiratory sensitization		
Band A	**Band C**	**Band E**
No evidence of respiratory sensitization	Mixed results	Positive evidence of respiratory sensitization

(Continued)

Table B-4 (Continued). Endpoint-specific criteria for the Tier 2 banding process.

Worksheet for respiratory sensitization endpoint

Respiratory sensitization (0 or 10 points possible)			
Data supports	**No evidence of respiratory sensitization (Band A)**	**Mixed results (Band C)**	**Respiratory sensitization based on totality of evidence (Band E)**
If data available, put in this row corresponding to the correct band criteria; otherwise leave blank.			
Source, Rank 1 or 2:			

Skin sensitization data sources

Endpoint	Rank	Source of information	Acronym
Skin Sensitization	1	NIOSH Skin Notation Profiles	SK Profiles
		European Chemicals Agency: Registration, Evaluation, Authorisation and Restriction of Chemicals	REACH
		Organization for Economic Co-operation and Development	OECD
		World Health Organization International Programme on Chemical Safety	WHO-IPCS
	2	Hazardous Substance Data Bank	HSDB

(Continued)

Table B-4 (Continued). Endpoint-specific criteria for the Tier 2 banding process.

Criteria for skin sensitization endpoint

NIOSH banding criteria for skin sensitization			
Test type	**Band A**	**Band C**	**Band E**
EC3 (%) (based on LLNA)	Non-skin sensitizer	EC3 (%) ≥2.0, ≤100 (weak to moderate skin sensitizer)	EC3 (%) ≤2.0 (strong to extreme skin sensitizer)
GPMT	No positive response or low incidence data	30% to 60% responding at >0.1% intradermal induction concentration or ≥30% responding at >1% intradermal induction concentration	≥30% responding at ≤0.1% intradermal induction concentration or ≥60% responding at >0.1% to ≤1% intradermal induction concentration
Buehler	No positive response or low incidence data	≥60% responding at >0.2 to ≤20% topical induction dose or ≥15% responding at >20% topical induction dose	≥15% responding at ≤0.2% topical induction concentration or ≥60% responding at any topical induction concentration
Qualitative	Negative results	Mixed results	Positive results or NIOSH SK-SEN notation*

NIOSH SK-SEN notation is used for substances identified as causing or contributing to allergic contact dermatitis (ACD) or other immune-mediated responses, such as airway hyper-reactivity (asthma) [NIOSH 2009].

Worksheet for skin sensitization

Skin sensitization (0 or 5 points possible)			
Data Supports	**Non-sensitizer (Band A)**	**Moderate sensitizer (Band C)**	**Extreme sensitizer (Band E)**
If data available, put data, calculations, notes, etc. in this row corresponding to the correct band criteria; otherwise leave blank.			
Source, Rank 1 or 2			

Table B-4 (Continued). Endpoint-specific criteria for the Tier 2 banding process.

Acute toxicity data sources

Endpoint	Rank	Source of Information	Acronym
Acute Toxicity	1	National Library of Medicine ChemID Plus	ChemID Plus
		U.S. EPA Superfund Chemical Data Matrix	EPA SCDM
		Pesticide Properties Database	PPDB
		World Health Organization International Programme on Chemical Safety	WHO-IPCS
	2	Hazardous Substance Data Bank	HSDB
		Agency for Toxic Substances and Disease Registry	ATSDR

Criteria for acute toxicity endpoint

NIOSH banding criteria for Acute Toxicity

Exposure/ dosing route	Band A	Band B	Band C	Band D	Band E
Oral toxicity (LD_{50})	>2,000 mg/kg-bodyweight	>300 to ≤2,000 mg/kg-bodyweight	>50 to ≤300 mg/kg-bodyweight	>5 to ≤50 mg/kg-bodyweight	≤5 mg/kg-bodyweight
Dermal toxicity (LD_{50})	>2,000 mg/kg-bodyweight	>1,000 to ≤2,000 mg/kg-bodyweight	>200 to ≤1,000 mg/kg-bodyweight	>50 to ≤200 mg/kg-bodyweight	≤50 mg/kg-bodyweight
Inhalation gases/vapors (LC_{50})	>20,000 ppm/4h	>2,500 to ≤20,000 ppm/4h	>500 to ≤2,500 ppm/4h	>100 to ≤500 ppm/4h	≤100 ppm/4h
Inhalation dust/ particles (LC_{50})	>5.0 mg/liter/4h	>1.0 to ≤5.0 mg/liter/4h	>0.5 to ≤1.0 mg/liter/4h	>0.05 to ≤0.5 mg/liter/4h	≤0.05 mg/liter/4h

Table B-4 (Continued). Endpoint-specific criteria for the Tier 2 banding process.

Worksheet for Acute Toxicity

Acute Toxicity (0 or 5 points possible)						
Data Supports		**A**	**B**	**C**	**D**	**E**
If data available, put in this row corresponding to the correct band criteria; otherwise leave blank.	Oral toxicity (LD_{50})					
	Dermal toxicity (LD_{50})					
	Inhalation gases/vapors (LC_{50})					
	Inhalation dust/particles (LC_{50})					
Source, Rank 1 or 2						

If multiple LD_{50} or LC_{50} values are found for each route of exposure/chemical state, record only the lowest value in this chart.

Skin corrosion/irritation data sources

Endpoint	Rank	Source of Information	Acronym
Skin Irritation	1	NIOSH Skin Notation Profiles	SK Profiles
		World Health Organization International Programme on Chemical Safety	WHO-IPCS
		European Chemicals Agency: Registration, Evaluation, Authorisation and Restriction of Chemicals	REACH
		Organization for Economic Co-operation and Development	OECD
	2	Agency for Toxic Substances and Disease Registry	ATSDR
		U.S. EPA Integrated Risk Information System	IRIS

Table B-4 (Continued). Endpoint-specific criteria for the Tier 2 banding process.

Criteria for Skin Corrosion/Irritation Endpoint

NIOSH Banding Criteria for Skin Corrosion/Irritation			
Band A	**Band B**	**Band C**	**Band E**
Non-irritating	Mild to moderate irritation	Moderate to severe irritation; reversible direct effects OR If results are mixed or indicate irritant potential with severity unspecified	Skin corrosion; irreversible effects pH value of <2.0 or >11.5

Worksheet for Skin Corrosion/Irritation Endpoint

Skin corrosion/irritation (0 or 5 points possible)				
Data supports	**Non-irritating (Band A)**	**Mild to moderate irritation; reversible direct effects (Band B)**	**Moderate to severe irritation; reversible effects or results are mixed or indicate irritant potential with severity unspecified (Band C)**	**Skin corrosion; irreversible effects or pH value ≤2.0 or >11.5 (Band E)**
If data available, put in this row corresponding to the correct band criteria; otherwise leave blank.				
Source, Rank 1 or 2				

Table B-4 (Continued). Endpoint-specific criteria for the Tier 2 banding process.

Eye damage/irritation data sources

Endpoint	Rank	Source of information	Acronym
Eye Damage/ Irritation	1	Organization for Economic Cooperation and Development	OECD
		World Health Organization International Programme on Chemical Safety	WHO-IPCS
		European Chemicals Agency: Registration, Evaluation, Authorisation and Restriction of Chemicals	REACH
	2	Agency for Toxic Substances and Disease Registry	ATSDR
		U.S. EPA Integrated Risk Information System	IRIS

Criteria for Eye Damage/Irritation Endpoint

NIOSH banding criteria for serious eye damage/irritation

Band A	Band B	Band C	Band E
Non-irritating	Mild to moderate irritation	Severe irritation; moderate to severe irritation or Irritant with unspecified severity, no conclusion, or mixed results	Irreversible eye damage

Table B-4 (Continued). Endpoint-specific criteria for the Tier 2 banding process.

Worksheet for Eye Damage/Irritation

Eye Damage/Irritation (0 or 5 points possible)				
Data Supports	**Non-irritating (A)**	**Mild to moderate irritation (B)**	**Severe irritation; moderate to severe irritation; or no classification system, no conclusion, or mixed results (C)**	**Irreversible eye damage (E)**
If data available, put in this row corresponding to the correct band criteria; otherwise leave blank.				
Source, Rank 1 or 2				

If using the e-Tool, this page will be automatically filled electronically upon insertion of relevant endpoint specific data. If filling out this table by hand, each of the preceding endpoint-specific tables in Section B.4 can be consulted to fill out this full table. The EDS for each health endpoint/toxicity parameter should be recorded in the EDS column and a final TDS should be calculated. The most stringent of all the bands entered is the final Tier 2 OEB for the chemical substance.

Table B-5. Full Table for Tier 2 Banding.

Chemical Name:

CAS number:

Endpoint	Data	EDS	Endpoint Band
Carcinogenicity	Source:		
Reproductive Toxicity	Source:		
Specific Target Organ Toxicity (STOT-RE)	Source:		
Genotoxicity	Source:		
Respiratory Sensitization	Source:		
Skin Sensitization	Source:		
Acute Toxicity	Source:		
Skin Corrosion/Irritation	Source:		
Eye Damage/Irritation	Source:		
Overall Tier 2 Band		TDS =	

The minimum TDS criteria are waived if any of the endpoint bands are E. In that case, the chemical substance is assigned an overall band E, regardless of TDS.

Appendix C
Examples of Chemical Substances Banded in Tier 1

This appendix provides examples of chemicals that NIOSH has banded with the Tier 1 process.

Chemical Name: Bentazone

Chemical Name: Bentazone
CAS number: 25057-89-0

Endpoint	Hazard code	Hazard category	H-code source	Endpoint band
Carcinogenicity				
Reproductive toxicity				
Specific target organ toxicity -				
Genotoxicity				
Respiratory and skin sensitization	H317	Category 1	GHS	C
Acute toxicity				
Inhalation				
Oral	H302	Category 4	GHS	C
Dermal				
Skin corrosion/irritation				
Eye damage/irritation	H319	Category 2	GHS	C
Most stringent band				**C**

Result: Band C is assigned as a result of the Tier 1 evaluation. A Tier 2 evaluation is recommended.
Data Source: GESTIS, http://www.dguv.de/ifa/gestis-database

Chemical Name: Perfluorooctane Sulfonic Acid

Chemical Name: Perfluorooctane Sulfonic Acid

CAS number: 1763-23-1

Endpoint	Hazard code	Hazard category	H-code source	Endpoint band
Carcinogenicity	H351	Category 2	GHS	E
Reproductive toxicity	H360D	Category 1B	GHS	D
Specific Target organ toxicity - repeated exposure	H372	Category 1	GHS	E
Genotoxicity				
Respiratory and skin sensitization				
Acute toxicity				
Inhalation	H332	Category 4	GHS	C
Oral	H302	Category 4	GHS	
Dermal				
Skin corrosion/irritation	H314	Category 1B	GHS	E
Eye damage/irritation				
Most stringent band				**E**

Result: Band E is assigned as a result of the Tier 1 evaluation. A Tier 2 evaluation is optional.
Data Source: GESTIS: http://www.dguv.de/ifa/gestis-database

Appendix D

Example of Chemical Substances Banded in Tier 2

This appendix provides an example of a chemical substance NIOSH has banded with the Tier 2 process.

Chemical Name: Benzo (k) Fluoranthene

CAS number: 207-08-09

- Toxicity information for benzo (k) fluoranthene was found for the following endpoints: carcinogenicity, genotoxicity, skin irritation, and eye irritation. Determinant scores were assigned as 30, 5, 5, and 5, respectively. No source data were found for reproductive toxicity, respiratory sensitization, skin sensitization, specific target organ toxicity, or acute toxicity. Here is the completed worksheet for the relevant health endpoints.

Carcinogenicity (0, 20, or 30 points possible)

	Band A	Band B	Band C	Band D	Band E
NTP/EPA/IARC/Canada/ California (QUALITATIVE)					EPA IRIS B2 – Probable human carcinogen – based on sufficient evidence of carcinogenic-ity in animals
US EPA IRIS Slope Factor					
US EPA IRIS Inhalation Unit Risk					
Health Canada TD_{05}					
Health Canada TC_{05}					
California Slope Factor				$1.2\ (mg/kg\text{-}day)^{-1}$	
California Inhalation Unit Risk				$1.1x10^{-4}\ (ug/m^3)^{-1}$	

- Cancer data were retrieved from EPA IRIS and Cal OEHHA. Because both qualitative and quantitative data were available, the quantitative data takes precedence for cancer.

The endpoint-specific band for cancer is therefore **band D**, based on the slope factor and inhalation unit risk values. A determinant score of 30 is assigned on the basis of presence of quantitative data.

Genotoxicity (0 or 5 points possible)

Data Supports	Negative Results (Band A)	Mixed Results (Band C)	Positive Results (Band E)
If data available, put in this row corresponding to the correct band criteria; otherwise leave blank.			Salmonella (023963) Completed: Positive
Source, Rank 1 or 2			NTP

- One positive in vivo result was found for genotoxicity. The endpoint-specific band for genotoxicity is band E, and a determinant score of 5 is assigned.

Skin Corrosion/Irritation (0 or 5 points possible)

Data Supports	Non-irritating (Band A)	Mild to moderate irritation; reversible direct effects (Band B)	Moderate to severe irritation; reversible effects or results are mixed or indicate irritant potential with severity unspecified (Band C)	Skin corrosion; irreversible effects or pH value ≤2.0 or >11.5 (Band E)
If data available, put in this row corresponding to the correct band criteria; otherwise leave blank.			Irritation, severity unspecified	
Source, Rank 1 or 2			ECHA/REACH	

- In the REACH database, benzo (k) fluoranthene is described as irritating to the skin, but the severity is not specified. Band C and a determinant score of 5 are assigned.

Eye Damage/Irritation (0 or 5 points possible)				
Data supports	**Non-irritating (Band A)**	**Mild to moderate irritation (Band B)**	**Severe irritation; moderate to severe irritation; or no classification system, no conclusion, or mixed results (Band C)**	**Irreversible eye damage (Band E)**
If data available, put in this row corresponding to the correct band criteria; otherwise leave blank.				
Source, Rank 1 or 2			HSDB	

- In the REACH database, benzo (k) fluoranthene is described as causing eye irritation and photosensitivity, but the severity is not specified. Band C is assigned, and a determinant score of 5 is assigned.

Result

Based on the available data, a TDS of 45 (30+5+5+5) is calculated. This TDS exceeds the threshold for data sufficiency (TDS ≥30). The most stringent band assigned is band E. The final Tier 2 band for benzo (k) fluoranthene is Band E, on the basis of genotoxicity.

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Appendix E

Chemical Substances Used for the Tier 1 Evaluation Exercise

The following chemical substances were used for the Tier 1 evaluation exercises described in Chapter 6.

1. 1,1,1,2,2-Pentafluoroethane
2. 1,1,1,2-Tetrafluoroethane
3. 1,1,1,3,3,3-Hexafluoropropane
4. 1,1,1,3,3-Pentafluoropropane
5. 1,1,1-Trifluoro-2,2-Dichloroethane
6. 1,1,1-Trifluoroethane
7. 1,1-Dichloro-1-fluoroethane
8. 1,1-Difluoroethane
9. 1,2-Epoxybutane
10. 1,3,3,3-Tetrafluoropropylene
11. 1,4-Hexadiene
12. 1,6-Hexanediamine
13. 1-Chloro-1, 1-Difluoroethane
14. 1-Decene
15. 1-Octanol
16. 1-Octene
17. 2,2,2-Trifluoroethanol
18. 2,3,3,3,-Tetrafluoropropene
19. 2,3,5,6-Tetrachloropyridine
20. 2,4-Dichlorophenol
21. 2,4-Toluene diamine and mixed isomers
22. 2-Chloro-1,1,1,2-Tetrafluoroethane
23. 2-Chloropropane
24. 2-Mercaptobenzothiazole
25. 2-Phosphono-1,2,4 butanetricarboxylic acid
26. 2-Picoline
27. 2-Propenoic acid, isooctyl ester
28. 3-Methoxypropylamine
29. 3-Picoline
30. 4-Picoline
31. Acetaldehyde
32. Acetic acid
33. Acetic anhydride
34. Acetone
35. Acetone cyanohydrin
36. Acetonitrile
37. Acetophenone
38. Acetylene tetrabromide
39. Acetylsalicylic acid
40. Acrylamide
41. Acrylic acid
42. Acrylic acid polymer
43. Acrylonitrile
44. Adipic acid
45. Adiponitrile
46. Aldicarb
47. Aldrin
48. Allyl alcohol
49. Allyl chloride
50. Allyl glycidyl ether
51. Allyl propyl disulfide
52. alpha-Methyl styrene
53. Aluminum - metal dust
54. Aluminum hydroxide
55. Aluminum oxide
56. Aminopyridine 2-
57. Aminotri (methylenephosphonic acid)
58. Amitrole
59. Ammonia
60. Ammonium chloride - fume
61. Ammonium perfluorooctanoate
62. Ammonium sulfamate
63. Aniline
64. Anisidine o-
65. Anisidine p-
66. Antimony - compounds (as Sb)
67. Antimony hydride [Stibine]
68. Antimony trioxide (as Sb)
69. ANTU
70. Arsenic - elemental
71. Arsenic pentoxide (as As)
72. Arsenous acid, arsenic acid and salts (as As)
73. Asphalt (Bitumen) fume
74. Atrazine
75. Azinphos-methyl - vapor and aerosol
76. Barium - soluble compounds (as Ba)
77. Barium chromate (as Cr)
78. Barium sulfate
79. Benomyl
80. Benzaldehyde
81. Benzene
82. Benzenesulfonic acid, 5-chloro-2((2-Hydroxy-1-napthalenyl)-azo)-4-methyl, barium salt (2:1)
83. Benzo[a]pyrene
84. Benzophenone
85. Benzoyl chloride
86. Benzoyl peroxide
87. Benzyl acetate
88. Benzyl alcohol
89. Benzyl chloride
90. Beryllium - compounds (as Be)
91. beta-Chloroprene
92. Biphenyl
93. bis-(2-chloroisopropyl) ether
94. Bis(2-dimethylaminoethyl) ether [DMAEE]
95. Bismuth telluride - undoped
96. Borates, tetra, sodium salts, anhydrous
97. Borates, tetra, sodium salts, decahydrate
98. Borates, tetra, sodium salts, pentahydrate
99. Boron oxide
100. Bromacil
101. Bromine
102. Bromine pentafluoride
103. Bromoform
104. Butadiene 1,3-
105. Butane
106. Butanol (+/-)-2-
107. Butanol n-
108. Butanol sec-
109. Butanol tert-
110. Butoxyethanol 2-
111. Butoxyethoxy) ethanol 2-(2-
112. Butoxyethyl acetate 2-
113. Butyl acetate n-
114. Butyl acetate sec-
115. Butyl acetate tert-

116. Butyl acrylate n-
117. Butyl chromate (as CrO3) tert-
118. Butyl glycidyl ether [BGE] n-
119. Butyl lactate n-
120. Butyl mercaptan n-
121. Butylamine n-
122. Butylamine sec-
123. Butylated hydroxytoluene [BHT] - vapor and aerosol
124. Butylbenzoic acid 4-tert-
125. Butylphenol o-sec-
126. Butylphenol p-tert-
127. Butyltoluene p-tert-
128. Butyraldehyde
129. Cadmium - metal and compounds (as Cd)
130. Calcium carbonate
131. Calcium chromate (as Cr)
132. Calcium cyanamide
133. Calcium cyanide (as CN)
134. Calcium hydroxide
135. Calcium oxide
136. Calcium silicate - synthetic
137. Calcium sulfate
138. Caprolactam - Vapor
139. Captafol
140. Captan
141. Carbaryl
142. Carbofuran
143. Carbon black
144. Carbon dioxide
145. Carbon disulfide
146. Carbon monoxide
147. Carbon tetrabromide
148. Carbon tetrachloride
149. Carbonyl fluoride
150. Catechol
151. Cellulose
152. Cesium hydroxide
153. Chloramphenicol
154. Chlordane
155. Chlordecone
156. Chlorinated camphene
157. Chlorinated diphenyl oxide o-
158. Chlorine
159. Chlorine dioxide
160. Chloro-1-nitropropane 1-
161. Chloro-1-propanol 2-
162. Chloro-2-methyl-2,3-dihydroisothiazol-3-one 5-
163. Chloro-2-propanol 1-
164. Chloroacetophenone 2-
165. Chloroacetyl chloride
166. Chlorobenzene
167. Chlorobenzylidene malononitrile o-
168. Chlorobromomethane
169. Chlorodifluoromethane [FC-22]
170. Chlorodiphenyl (42% chloride)
171. Chlorodiphenyl (54% chloride)
172. Chloroform
173. Chloromethyl) ether bis
174. Chloropentafluoroethane
175. Chloropicrin
176. Chloropropionic acid 2-
177. Chlorostyrene o-
178. Chlorotoluene o-
179. Chlorotrifluoroethylene
180. Chlorotrifluoromethane [FC-13]
181. Chlorpyrifos
182. Chromic acid and chromates (as CrO_3)
183. Chromium (VI) compounds (as Cr)
184. Chrysene
185. Clopidol
186. Coal tar pitch volatiles -as benzene-sol, aerosol
187. Cobalt - elemental/metal
188. Cobalt carbonyl (as Co)
189. Cobalt hydrocarbonyl (as Co)
190. Copper - fume (as Cu)
191. Cresol - mixture of isomers
192. Cresol m-
193. Cresol o-
194. Cresol p-
195. Crotonaldehyde
196. Crufomate
197. Cumene
198. Cumene hydroperoxide
199. Cyanamide
200. Cyanogen
201. Cyclohexane
202. Cyclohexanol
203. Cyclohexanone
204. Cyclohexene
205. Cyclohexylamine
206. Cyclonite
207. Cyclopentadiene
208. Cyclopentane
209. Cyhexatin
210. DDT [Dichlorodiphenyl-trichloroethane]
211. Decaborane
212. Decabromodiphenyl oxide
213. Dehydrolinalool
214. Demeton - vapor and aerosol
215. Demeton-S-methyl - vapor and aerosol
216. Di(2-ethylhexyl)phthalate [DEHP]
217. Diacetone alcohol
218. Diallylamine
219. Diazinon
220. Diazomethane
221. Diborane
222. Dibromo-3-chloropropane 1,2-
223. Dibromoneopentyl glycol
224. Dibutyl phenyl phosphate
225. Dibutyl phosphate
226. Dibutyl phthalate
227. Dibutylaminoethanol 2-N-
228. Dichloro-1-nitroethane 1,1-
229. Dichloro-2-butene 1,4-
230. Dichloro-5,5-dimethyl hydantoin 1,3-
231. Dichlorobenzene o-
232. Dichlorobenzene p-
233. Dichlorodifluoro-methane [FC-12]
234. Dichloroethane 1,1-
235. Dichloroethyl ether
236. Dichloroethylene, cis-isomer 1-2
237. Dichloroethylene, sym-isomer 1-2
238. Dichloroethylene, trans-isomer 1,2-
239. Dichlorofluoromethane [FC-21]
240. Dichloromethane
241. Dichlorophenoxyacetic [2,4-acid] 2,4-D
242. Dichloropropene 1,3-
243. Dichloropropionic acid 2,2-
244. Dichlorotetrafluoro-ethane [Cryofluorane]
245. Dichlorvos [DDVP] - vapor and aerosol
246. Dicrotophos - vapor and aerosol
247. Dicyclopentadiene
248. Dicyclopentadienyl iron
249. Dieldrin
250. Diesel fuel - vapor and aerosol
251. Diesel fuel No. 2 - vapor and aerosol
252. Diesel fuel No. 4 - vapor and aerosol
253. Diethanolamine
254. Diethyl ketone
255. Diethyl phthalate
256. Diethylamine
257. Diethylaminoethanol 2-
258. Diethylbenzenes, mixed isomers
259. Diethylene glycol
260. Diethylene glycol monoethyl ether
261. Diethylene triamine
262. Difluorodibromo-methane
263. Difluoromethane
264. Diglycidyl ether [DGE]
265. Diisobutyl ketone
266. Diisobutylene
267. Diisopropylamine
268. Dimethyl ether

269. Dimethyl ethylamine N,N-
270. Dimethyl phthalate
271. Dimethyl sulfate
272. Dimethyl sulfoxide
273. Dimethyl terephthalate
274. Dimethylacetamide N,N-
275. Dimethylamine
276. Dimethylaniline
277. Dimethylbutane 2,2-
278. Dimethylbutane 2,3-
279. Dimethylethoxysilane
280. Dimethylformamide
281. Dimethylhydrazine 1,1-
282. Dinitolmide
283. Dinitrobenzene m-
284. Dinitrobenzene o-
285. Dinitrobenzene p-
286. Dinitro-o-cresol
287. Dinitrotoluene
288. Dinitrotoluene 2,4-
289. Dinitrotoluene 3,5-
290. Dioxane 1,4-
291. Dioxathion - vapor and aerosol
292. Dioxolane 1,3-
293. Diphenyl ether/biphenyl mixture (vapor)
294. Diphenylamine
295. Dipropyl ketone
296. Diquat
297. Disulfiram
298. Disulfoton - vapor and aerosol
299. Diuron
300. Divinyl benzene
301. d-Limonene
302. Dowtherm Q
303. Emery
304. Endosulfan
305. Endrin
306. Enflurane
307. Epichlorohydrin
308. EPN
309. Erythromycin
310. Ethanol
311. Ethanolamine
312. Ethion
313. Ethoxyethanol [EGEE] 2-
314. Ethoxyethyl acetate [EGEEA] 2-
315. Ethyl acetate
316. Ethyl acrylate
317. Ethyl amyl ketone
318. Ethyl benzene
319. Ethyl bromide
320. Ethyl butyl ketone
321. Ethyl chloride
322. Ethyl cyanoacrylate
323. Ethyl ether
324. Ethyl formate
325. Ethyl mercaptan
326. Ethyl silicate
327. Ethyl tert-butyl ether [ETBE]
328. Ethylamine
329. Ethylene chlorohydrin
330. Ethylene dibromide
331. Ethylene dichloride
332. Ethylene glycol
333. Ethylene oxide
334. Ethylenediamine
335. Ethylenimine
336. Ethylhexanoic acid - vapor and aerosol 2-
337. Ethylhexanol 2-
338. Ethylmorpholine N-
339. Fenamiphos
340. Fensulfothion
341. Fenthion
342. Ferbam
343. Ferrovanadium - dust
344. Fluorine
345. Fonofos
346. Formaldehyde
347. Formamide
348. Formic acid
349. Furfural
350. Furfuryl alcohol
351. Gallium arsenide
352. Gasoline
353. Germanium tetrahydride
354. Glutaraldehyde
355. Glycerin - mist
356. Glycidol
357. Glycidyl methacrylate
358. Glyoxal
359. Graphite
360. Graphite - all forms except graphite fibers
361. Gypsum
362. Hafnium and compounds, as Hf
363. Halothane
364. Heptachlor
365. Heptachlor epoxide
366. Heptane n-
367. Hexachlorobenzene [HCB]
368. Hexachlorobutadiene
369. Hexachlorocyclohexane alpha-
370. Hexachlorocyclohexane beta-
371. Hexachlorocyclo-pentadiene
372. Hexachloroethane
373. Hexachloronaphthalene
374. Hexafluoroacetone
375. Hexamethylene diisocyanate [HDI] 1,6
376. Hexamethylene glycol
377. Hexane n-
378. Hexanediol diacrylate
379. Hexene 1-
380. Hexyl acetate sec-
381. Hexylene glycol
382. HFE-7100
383. Hydrazine
384. Hydrazoic acid
385. Hydrogen bromide
386. Hydrogen chloride
387. Hydrogen cyanide (as CN)
388. Hydrogen fluoride
389. Hydrogen peroxide
390. Hydrogen selenide
391. Hydrogen sulfide
392. Hydrogenated terphenyls - nonirradiated
393. Hydroquinone
394. Hydroxybenzoic acid
395. Hydroxypropyl acrylate 2-
396. Indene
397. Indium and compounds (as In)
398. Iodine
399. Iodoform
400. Iron oxide [Fe2O3] - dust (as Fe)
401. Iron pentacarbonyl
402. Isoamyl alcohol
403. Isobutane
404. Isobutyl acetate
405. Isobutyl alcohol
406. Isobutylamine
407. Isobutyraldehyde
408. Isobutyronitrile
409. Isocyanuric acid
410. Isooctane
411. Isooctyl alcohol
412. Isopentane
413. Isopentyl acetate
414. Isophorone
415. Isophorone diisocyanate
416. Isophthalic acid
417. Isoprene
418. Isopropanol [isopropyl alcohol]
419. Isopropoxyethanol 2-
420. Isopropyl acetate
421. Isopropyl ether
422. Isopropyl glycidyl ether [IGE]
423. Isopropylamine
424. Isopropylaniline N-
425. Kaolin
426. Kerosene
427. Ketene
428. Lead - elemental and inorganic compounds (as Pb)
429. Lead arsenate (as As)
430. Lead chromate (as Cr)
431. Lead phosphate (as Pb)
432. Lindane
433. Liquified petroleum gas [LPG]
434. Lithium hydride

435. Magnesite
436. Magnesium oxide - Fume
437. Malathion
438. Maleic anhydride
439. Malononitrile
440. Mancozeb
441. Manganese - elemental and inorganic compounds (as Mn)
442. Manganese cyclopentadienyl tricarbonyl (as Mn)
443. Manganese tetroxide (as Mn)
444. Melamine
445. Mercaptoethanol
446. Mercury - alkyl compounds (as Hg)
447. Mesityl oxide
448. Methacrylic acid
449. Methanol
450. Methomyl
451. Methoxy-1-propanol 2-
452. Methoxy-1-propyl acetate 2-
453. Methoxy-2-propanol [PGME] 1-
454. Methoxyacetic acid
455. Methoxychlor
456. Methoxyethanol 2-
457. Methoxyethyl acetate 2-
458. Methoxyethyl ether bis(2-
459. Methoxyphenol 4-
460. 2-Methoxypropyl ether [DPGME] bis,
461. Methyl 2-cyanoacrylate
462. Methyl acetate
463. Methyl acetylene
464. Methyl acetylene-propadiene mixture [MAPP]
465. Methyl acrylate
466. Methyl aniline N-
467. Methyl bromide
468. Methyl chloride
469. Methyl chloroacetate
470. Methyl chloroform
471. Methyl demeton
472. Methyl ethyl ketone [MEK]
473. Methyl ethyl ketone peroxide [MEKP]
474. Methyl ethyl ketoxime
475. Methyl formate
476. Methyl hydrazine
477. Methyl iodide
478. Methyl isoamyl ketone
479. Methyl isobutyl carbinol
480. Methyl isobutyl ketone
481. Methyl isocyanate
482. Methyl isopropyl ketone
483. Methyl mercaptan
484. Methyl mercury (as Hg)
485. Methyl methacrylate
486. Methyl n-amyl ketone
487. Methyl n-butyl ketone
488. Methyl parathion
489. Methyl pentane 2-
490. Methyl pentane 3-
491. Methyl propyl ketone
492. Methyl silicate
493. Methyl tert-butyl ether [MTBE]
494. Methylacrylonitrile
495. Methylal
496. Methylamine
497. Methylbutyl acetate 2-
498. Methylcyclohexane
499. Methylcyclohexanol
500. Methylcyclohexanone o-
501. Methylcyclopentadienyl manganese tricarbonyl 2-
502. Methylene bis(4-cyclohexyliso-cyanate)
503. Methylene bisphenyl isocyanate [MDI]
504. Methylene dianiline 4,4'-
505. Metribuzin
506. Mevinphos
507. Mica
508. Molybdenum - soluble compounds (as Mo)
509. Monochloroacetic acid
510. Monocrotophos - vapor and aerosol
511. Morpholine
512. m-Xylene alpha,alpha'-diamine
513. n,n-Dimethyl-para-toluidine
514. Naled - vapor and aerosol
515. n-Amyl alcohol
516. Naphthalene
517. Naphthalene diisocyanate [NDI]
518. n-Hexyl alcohol
519. Nickel - soluble inorganic compounds (as Ni)
520. Nickel carbonyl (as Ni)
521. Nickel chloride (as Ni)
522. Nickel dioxide
523. Nickel oxide
524. Nickel sesquioxide
525. Nickel subsulfide (as Ni)
526. Nickel sulfate (as Ni)
527. Nickelous carbonate
528. Nickelous hydroxide (as Ni)
529. Nicotine
530. Nitrapyrin
531. Nitric acid
532. Nitric oxide
533. Nitroaniline p-
534. Nitrobenzene
535. 4-(2-Nitrobutyl) morpholine
536. Nitrochlorobenzene p-
537. Nitroethane
538. Nitrogen dioxide
539. Nitrogen trifluoride
540. Nitroglycerin [NG]
541. Nitromethane
542. Nitropropane 1-
543. Nitropropane 2-
544. Nitrotoluene m-
545. Nitrotoluene o-
546. Nitrotoluene p-
547. Nitrous oxide
548. N-Methyl-2-Pyrrolidone
549. Nonane - all isomers
550. Octachloronaphthalene
551. Octane n-
552. Octyl-4-isothiazolin-3-one 2-
553. Osmium tetroxide
554. Oxalic acid
555. Oxybis(benzenesulfonyl hydrazide) p,p'-
556. Oxygen difluoride
557. Ozone - Heavy work
558. para-Aminobenzoic acid
559. Paraffin wax - fume
560. Paraquat
561. Paraquat dichloride
562. Paraquat dimethyl sulfate
563. Parathion
564. Pentaborane
565. Pentachloroethane
566. Pentachloronaphthalene
567. Pentachloronitrobenzene
568. Pentachlorophenol
569. Pentaerythritol
570. Pentaerythritol triacrylate
571. Pentane n-
572. Pentyl acetate 1-
573. Pentyl acetate 2-
574. Pentyl acetate 3-
575. Pentyl acetate tert-
576. Perchloromethyl mercaptan
577. Perchloryl fluoride
578. Perlite
579. Petroleum distillates [Naphtha]
580. Phenol
581. Phenothiazine
582. Phenoxyethanol 2-
583. Phenyl ether - vapor
584. Phenyl glycidyl ether [PGE]
585. Phenyl mercaptan
586. Phenylenediamine m-
587. Phenylenediamine o-
588. Phenylenediamine p-
589. Phenylhydrazine
590. Phorate
591. Phosgene
592. Phosphine
593. Phosphoric acid
594. Phosphorus (yellow)

595. Phosphorus oxychloride
596. Phosphorus pentachloride
597. Phosphorus pentasulfide
598. Phosphorus pentoxide
599. Phosphorus trichloride
600. Phthalic anhydride
601. Phthalodinitrile m-
602. Picloram
603. Picric acid
604. Pindone
605. Piperazine dihydrochloride
606. Piperidine
607. Plaster of Paris
608. Platinum - metal
609. Polyethylene glycols (MW > 200)
610. Polypropylene glycols
611. Polyvinyl chloride [PVC]
612. Portland cement
613. Potassium bromate
614. Potassium cyanide (as CN)
615. Propane
616. Propanol n-
617. Propargyl alcohol
618. Propargyl bromide
619. Propiolactone beta-
620. Propionaldehyde
621. Propionic acid
622. Propionitrile
623. Propoxur
624. Propoxyethanol 2-
625. Propoxyethyl acetate 2-
626. Propyl acetate n-
627. Propyl nitrate n-
628. Propylene dichloride
629. Propylene glycol
630. Propylene glycol dinitrate
631. Propylene glycol monomethyl ether acetate
632. Propylene imine
633. Propylene oxide
634. Pyrethrum
635. Pyridine
636. Quinoline
637. Quinone
638. Resorcinol
639. Rhodium - soluble compounds (as Rh)
640. Ronnel [Fenchlorphos]
641. Rotenone (commercial)
642. Rubber solvent (Naphtha)
643. Selenium - inorganic compounds (as Se)
644. Selenium hexafluoride
645. Selenium sulfide (as Se)
646. Sesone
647. Silica, amorphous - diatomaceous earth (calcined)
648. Silica, amorphous - fused
649. Silica, amorphous - precipitated and gel
650. Silica, amorphus - diatomaceous earth (uncalcined)
651. Silica, crystalline - cristobalite
652. Silica, crystalline - quartz
653. Silica, crystalline - tridymite
654. Silica, crystalline - Tripoli
655. Silicon
656. Silicon carbide
657. Silicon tetrahydride [Silane]
658. Silver - soluble compounds (as Ag)
659. Sodium azide
660. Sodium bisulfite
661. Sodium chloroacetate
662. Sodium cyanide (as CN)
663. Sodium diethyldithiocarbamate
664. Sodium fluoroacetate
665. Sodium hydroxide
666. Sodium metabisulfite
667. Sodium persulfate (as S2O8)
668. Sodium pyridinethione
669. Sodium pyrithione
670. Stannous oxide (as Sn)
671. Starch
672. Strontium chromate (as Cr)
673. Strychnine
674. Styrene - monomer
675. Subtilisins [proteolytic enzymes]
676. Succinonitrile
677. Sucrose
678. Sulfometuron methyl
679. Sulfotep [TEDP]
680. Sulfur dioxide
681. Sulfur hexafluoride
682. Sulfur monochloride
683. Sulfur pentafluoride
684. Sulfuric acid
685. Sulfuryl fluoride
686. Sulprofos
687. Talc - containing no asbestos fibers
688. Tantalum - metal
689. Tantalum oxide - dust (as Ta)
690. Tellurium - compounds (as Te)
691. Tellurium hexafluoride
692. Temephos
693. TEPP [Tetraethyl pyrophosphate]
694. Terbufos - vapor and aerosol
695. Terephthalic acid
696. Terphenyl - mixed isomers
697. tert-Amyl methyl ether [TAME]
698. tert-Pentane [Neopentane]
699. Tetrachloro-1,2-difluoroethane [FC-112] 1,1,2,2-
700. Tetrachloro-2,2-difluoroethane [FC-11 2a] 1,1,1,2-
701. Tetrachloroethane 1,1,2,2-
702. Tetrachloroethylene [perchloroethylene]
703. Tetrachloronaphthalene
704. Tetraethyl lead (as Pb)
705. Tetraethylene glycol diacrylate
706. Tetraethylene pentamine
707. Tetrafluoroethylene
708. Tetrahydrofuran
709. Tetrahydrofurfuryl-alcohol
710. Tetramethyl lead (as Pb)
711. Tetramethyl succinonitrile
712. Tetranitromethane
713. Tetrasodium pyrophosphate
714. Tetryl
715. Thallium - soluble compounds (as Tl)
716. Thimerosal
717. Thiobis(6-tert-butyl-m-cresol) 4,4'-
718. Thioglycolic acid
719. Thiram
720. Tin - metal
721. Tin - organic compounds (as Sn)
722. Tin dioxide (as Sn)
723. Titanium tetrachloride
724. Toluene
725. Toluene-2,4-diisocyanate[2,4-TDI]
726. Toluidine m-
727. Toluidine o-
728. Toluidine p-
729. Tributyl phosphate
730. Tributyl tin benzoate (as TBTO)
731. Tributyltin fluoride (as TBTO)
732. Tributyltin linoleate (as TBTO)
733. Tributyltin methacrylate (as TBTO)
734. Tributyltin naphthenate (as TBTO)
735. Trichloro-1,2,2-trifluoroethane [FC-113] 1,1,2-
736. Trichloroacetic acid
737. Trichlorobenzene - all isomers
738. Trichlorobenzene 1,2,3-
739. Trichlorobenzene 1,3,5-
740. Trichloroethane 1,1,2-
741. Trichloroethylene
742. Trichlorofluoromethane [FC-11]
743. Trichloronaphthalene
744. [2,4,5-Trichlorophenoxyacetic acid] 2,4,5-T
745. Trichloropropane 1,2,3-
746. Triethanolamine

747. Triethoxysilane
748. Triethylamine
749. Triethylene glycol diacrylate
750. Triethylenetetramine
751. Triethylphosphate
752. Trifluorobromomethane [F-13B1]
753. Triglycidyl-s-triazinetrione 1,3,5-
754. Trimellitic anhydride
755. Trimethoxysilane
756. Trimethyl benzene [Mesitylene] 1,3,5-
757. Trimethyl benzene 1,2,3-
758. Trimethyl benzene 1,2,4-
759. Trimethyl phosphite
760. Trimethylamine
761. Trimethylolpropane trimethacrylate
762. Trimethylolpropane-triacrylate
763. Tri-n-butyltin chloride (as TBTO)
764. bis(Tri-n-butyltin oxide) [TBTO] (as TBTO)
765. Trinitrotoluene [TNT] 2,4,6-
766. Triorthocresyl phosphate
767. Triphenyl amine
768. Triphenyl phosphate
769. Tungsten - insoluble compounds (as W)
770. Tungsten carbide - containing >2% cobalt, as Co
771. Turpentine
772. Uranium (natural) - insoluble compounds (as U)
773. Urea
774. Valeraldehyde n-
775. Vanadium pentoxide - fume (as V_2O_5)
776. Vanillin
777. Vinyl acetate
778. Vinyl bromide
779. Vinyl chloride
780. Vinyl cyclohexene dioxide
781. Vinyl fluoride
782. Vinyl toluene [methyl styrene] - mixed isomers
783. Vinylcyclohexene
784. Vinylidene chloride
785. Vinylidene fluoride
786. Warfarin
787. Xylene - mixed isomers
788. Xylene m-
789. Xylene o-
790. Xylene p-
791. Xylidine - mixed isomers (vapor and aerosol)
792. Yttrium - compounds (as Y)
793. Zinc beryllium silicate (as Be)
794. Zinc chloride - fume
795. Zinc chromate (as Cr)
796. Zinc oxide - dust
797. Zinc potassium chromate (as Cr)
798. Zinc stearate
799. Zinc yellow (as Cr)
800. Zirconium - compounds (as Zr)

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Promoting productive workplaces through safety and health research

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