The NIOSH Occupational Exposure Banding Process: Guidance for the Evaluation of Chemical Hazards

External Review Draft

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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; Schulte et al. 2010; Nikfar and Malekirad 2014; Deveau et al. 2015; 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 Environmental Protection Agency (EPA), the Toxic Substances Control Act (TSCA) Chemical Substance Inventory currently contains over 85,000 chemicals that are commercially available [EPA 2015] yet only about 1,000 of these chemicals have been assigned an authoritative (government, consensus, or peer reviewed) OEL. Furthermore, the rate at which new chemicals are being introduced into commerce significantly outpaces OEL development, creating a need for guidance on thousands of chemicals that lack reliable exposure limits [Michaels 2014]. Occupational exposure banding, also known as hazard banding or health hazard banding, is a systematic process that uses both qualitative and quantitative hazard information on selected health effect endpoints to identify potential exposure ranges or categories. **The NIOSH occupational exposure banding process seeks to create a consistent and documented process to characterize chemical hazards so timely and well-informed risk management decisions can be made for chemicals lacking OELs.**

The concept of using hazard-based categories to communicate potential health concerns, signal workers and employers 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. Such systems are deeply embedded in occupational hygiene practice, particularly in the pharmaceutical industry [Naumann et al. 1996; NIOSH 2009c], and are also elements of well-developed, modern hazard communication programs (e.g., United Nations 2013 Globally Harmonized System of Classification and Labelling of Chemicals). 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 utilize the process, (2) determination of potential health impacts based on nine toxicological endpoints separately, (3) hazard-based categories linked to quantitative exposure ranges, and (4) assessment of the process via extensive evaluation exercises to determine accuracy and repeatability.

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. While 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 of interest and to quickly identify toxic chemicals that should be considered for substitution or elimination. Tier 1 would likely be most be appropriate when banding a large amount of chemicals and deciding which ones should be prioritized

for elimination or substitution. In general, Tier 1 can be used as a quick screening method, but NIOSH recommends going to Tier 2 if the user expertise and data are available. It should be noted that if the Tier 1 evaluation results in a band E, 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 into a different band. 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.

The NIOSH occupational exposure banding process considers the health effects associated with nine standard toxicological health endpoints. Endpoints evaluated include acute toxicity, skin corrosion and irritation, serious eye damage and irritation, respiratory sensitization, skin sensitization, genotoxicity, carcinogenicity, reproductive/developmental toxicity, and specific target organ toxicity resulting from repeated exposure. The process looks at each health endpoint separately for each chemical, and the endpoint bands allow the user to make judgements about which health effects are the primary concern for workers who are exposed. This type of specificity allows users to customize their control strategies based on both the potency of the chemical and the target organ/health effect. In Tier 1, respiratory and skin sensitization are considered together as one endpoint due to the construction of the H-codes, which are alphanumeric codes used in the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) to designate hazards.

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 chemicals into one of five bands ranging from A through E. These bands, or OEBs, define the range of exposures expected to protect worker health. Band E represents the lowest exposure concentration range recommendation, while 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 referred to as more "protective" than bands that represent higher exposure ranges.

The occupational exposure banding process can be used to identify potential health effects and target organs, identify health risks that impact health communication, inform decisions regarding control interventions, inform medical surveillance decisions, and provide critical information quickly. One major benefit of occupational exposure banding is that the amount of time and data required to categorize a chemical into an OEB is far less than that required to develop an OEL. However, there is greater uncertainty as to whether the OEB is as protective as an OEL produced by a rigorous risk assessment process. **An OEB is not meant to replace an OEL, rather it serves as a starting point to inform risk management decisions.** An OEB can also assist with prioritization of chemicals for which an OEL should be developed.

NIOSH has performed evaluation exercises to ensure the accuracy and repeatability of the occupational exposure banding process. To evaluate the Tier 1 process, NIOSH compared the OELs of 600 chemicals to the Tier 1 band for those chemicals. This evaluation found that the NIOSH Tier 1 banding process resulted in a band that included the OEL or was more protective than the OEL for 91.5% of chemicals. Five iterative phases of Tier 2 reliability testing were performed to assess Tier 2 as the methodology evolved. These assessments involved over 130 unique chemicals. Results of these evaluations show that Tier 2 OEBs appropriately reflect the toxicity of a chemical. Tier 2 OEBs include the OEL or are more protective than the OEL for 98% of chemicals tested. In summary, the results from the evaluation exercises demonstrate that the occupational exposure banding process operates as expected, and can be a useful tool to evaluate chemicals without OELs. Special consideration should be given when banding substances comprised of a mixture of two or more chemicals. Other situations that warrant special considerations, such as nanoparticles, are described in detail in this document.

The number of chemicals that lack authoritative OELs is substantial, and risk management guidance for these chemicals is needed. Occupational exposure banding is one additional tool that can be used to provide guidance. An OEB provides more than a range of exposures that is expected to be protective of worker health. Rather, an OEB can be utilized to identify potential health effects and target organs, identify health risks that affect health communication, inform implementation of control interventions and preparedness plans, inform medical surveillance decisions, and provide critical information quickly. This document fully details the use and application of this process and provides a summary of efforts taken to evaluate its effectiveness and usability.

Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists®
ATSDR	Agency for Toxic Substances and Disease Registry
BMD	Benchmark Dose
BMCL	Benchmark Concentration Lower Bound
BMDL	Benchmark Dose Lower Bound
CalEPA	California Environmental Protection Agency
CalOEHHA	State of California Office of Environmental Health Hazard Assessment
Cal/OSHA	California Occupational Safety and Health Administration
CAS	Chemical Abstract Service
CFR	Code of Federal Regulations
CICADs	Concise International Chemical Assessment Documents
DNEL	Derived No Effect Level
EDS	Endpoint Determinant Score
EHC	Environmental Health Criteria
ECHA	European Chemicals Agency
ER GV	Emergency Response Guide Value
EU	European Union
GHS	Globally Harmonized System of Classification and Labelling of Chemicals
GPMT	Guinea Pig Maximization Test
H-code	Hazard Code
HCS	Hazard Communication Standard
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
ISO	International Standards Organization
ITER	International Toxicity Estimates for Risk
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
mg/kg	Milligrams per Kilogram
mg/m^3	Milligrams per Cubic Meter of Air
MRL	Minimal Risk Level
NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
NOAEL	No Observed Adverse Effect Level
NTP	National Toxicology Program
OEB	Occupational Exposure Band
OEB_{ER}	Emergency Response Band
OECD	Organisation for Economic Cooperation and Development
OEL	Occupational Exposure Limit
OSHA	Occupational Safety and Health Administration
PEL	Permissible Exposure Limit
POD	Point of Departure
ppm	Parts per Million
REACH	Registration, Evaluation, Authorization and Restriction of Chemicals (European Chemicals Agency)
REL	Recommended Exposure Limit
RfC	Reference Concentration
RfD	Reference Dose
RoC	U.S. National Toxicology Program Report on Carcinogens
SDS	Safety Data Sheet
SF	Slope Factor
SIDS	Screening Information Dataset
STOT-RE	Specific Target Organ Toxicity-Repeated Exposure
TC_{05}	Tumorigenic Concentration for 5% of the population

1	TD_{05}	Tumorigenic Dose for 5% of the population
2	TDC	Tolerable Daily Concentration
3	TDI	Tolerable Daily Intake
4	TDS	Total Determinant Score
5	TI	Tolerable Intake
6	TLV	Threshold Limit Value®
7	TWA	Time-Weighted Average
8	U.S. EPA	U.S. Environmental Protection Agency
9	WEEL	Workplace Environmental Exposure Level®
10	WHO	World Health Organization

Glossary

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

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

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 based on combinations of hazard and exposure information. The following four main control bands have been developed for exposure to chemicals 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

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 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 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 database of the German Social Accident Insurance that contains approximately 8,000 chemicals 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 or chemical mixture, including, where appropriate, the degree of hazard

Mixture: solutions composed of two or more substances in which they 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 using 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 limit: Levels of exposure that most employees may be exposed to for up to 10 hours per day, 40 hours per week, for a working lifetime, without experiencing adverse health effects.

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, while in itself is not necessarily combustible, may, generally by yielding oxygen, cause or contribute to the combustion of other material

Oxidizing solid: a solid that, while in itself not necessarily combustible, 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 inhalation of the substance

Self-heating substance: a solid or liquid, other than a pyrophoric substance, which, by reaction with air and without energy supply, is liable to self-heat. 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, which 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 will 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 (GHS) that can impair function, both reversible and irreversible, immediate and/or delayed after repeated exposure to a substance

Specific target organ toxicity – single exposure: all significant health effects, not otherwise specifically included in the GHS that can impair function, both reversible and irreversible, immediate and/or delayed after a single exposure to a substance

Substance: a chemical element and its compounds in the natural state or obtained by any production process, including any additive necessary to preserve the stability of the product and any impurities deriving from the process used, but excluding any solvent that may be separated without affecting the stability of the substance or changing its composition

Substances that, in contact with water emit flammable gases: solids or liquids that, by interaction with water, are liable to become spontaneously flammable or to give off flammable gases in dangerous quantities

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 component 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 dataset as sufficient for banding in Tier 2.

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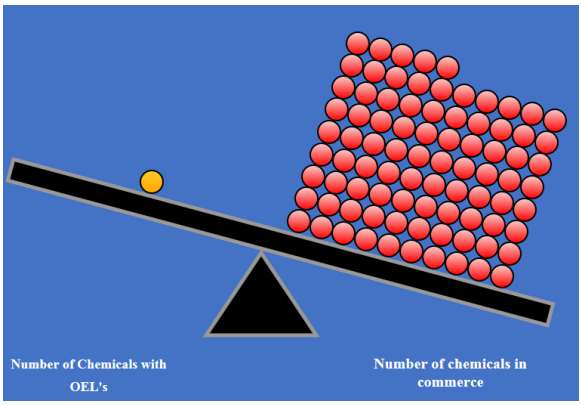
Chapter 1 : Introduction to Occupational Exposure Banding

1.0. Occupational Exposure Banding: Definition

Occupational exposure limits (OELs) have been an important component of the practice of occupational hygiene for decades [Cook 1987; Schulte et al. 2010; Nikfar and Malekirad 2014; Deveau et al. 2015; Skowroń and Czerczak 2015]. Occupational hygienists develop and implement control strategies largely based on the relevant OELs that are available to them. Exposures to chemicals at concentrations above their OEL are considered unsafe, and hygienists act to ensure that workers are not exposed to concentrations of hazardous chemicals that exceed their designated OELs. Unfortunately, the rate that chemicals have been introduced into commerce has significantly outpaced the development of authoritative (i.e., governmental, consensus, or peer reviewed) OELs [Michaels 2014]. The U.S. Environmental Protection Agency (EPA) reports that the Toxic Substances Control Act (TSCA) Chemical Substance Inventory contains over 85,000 chemicals [EPA 2015], yet only about 1,000 chemicals 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 existing OELs, guidance for the thousands of chemicals that currently lack reliable exposure limits is needed. 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 exposures expected to be protective of worker health. Thus, occupational exposure banding is one of a number of strategies used to address worker and responder safety and health when the time, data, and resources needed for OEL development are not available.

Figure 1-1: Chemicals in Commerce vs. Chemicals with Occupational Exposure Limits



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 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 agent in the work environment. For chemical compounds, exposure can occur through inhalation, ingestion, or through 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. Chemical hazards have the potential to cause harm or adverse effects to individuals who are exposed to them. The purpose of occupational exposure banding is to reduce the risk to workers who are exposed to chemicals in the workplace. Risk is defined as the probability that a person will experience adverse effects after exposure to chemical hazards. 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 even to inform exposure control requirements is not new. Numerous hazard classification and category-based systems have seen extensive use in the occupational setting [Zalk and Nelson 2008; Egeghy et al. 2011; Shin et al. 2014]. Such systems are deeply embedded in occupational hygiene practice, particularly in the pharmaceutical industry, 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 chemical hazards has been in the form of OELs rather than OEBs. The science and art of evaluating chemical hazards 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]. Despite this history, derivation of OELs remains a resource intensive process driven by the need for exposure data, toxicology data, risk assessment methodology, and other considerations [Schulte et al. 2010]. Consequently, the number of chemicals 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 1000 chemicals. In many cases, multiple organizations have assigned different OELs to the same chemical, making the number of chemicals that have been assigned an OEL even fewer. At the same time, the Occupational Safety and Health Administration (OSHA) has estimated that 80,000 hazardous chemicals are currently used in the United States, and over 40 million employees are now potentially exposed to hazardous chemicals in over 5 million workplaces [OSHA 2012]. The characterization of the potential adverse health effects of chemical and

physical agents is one of the foundations of occupational hygiene as a public health practice [OSHA 1998]. Therefore, strategies for expedited assessment and characterization of chemical hazards are needed to inform occupational risk management decisions.

The National Institute for Occupational Safety and Health (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 severity of health outcomes (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 chemicals have the lowest health hazard potential (and thus higher exposure ranges), and band E chemicals have the highest recognized health hazard potential Figure 1-2[McKernan et al. 2016].

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

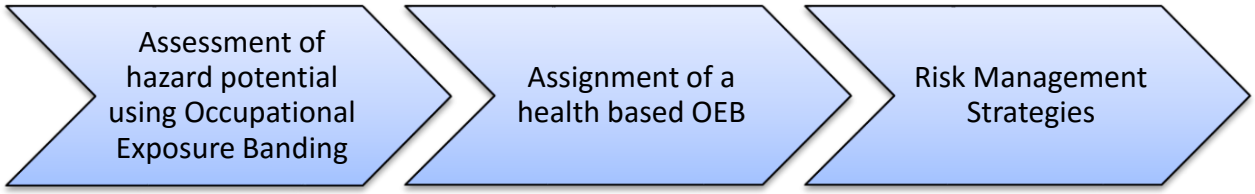
Occupational exposure banding aligns with the professional practice framework of anticipation, recognition, evaluation, control, and confirmation of protection from health hazards [Laszcz-Davis et al. 2014; Jahn et al. 2015]. Furthermore, occupational exposure banding will assist in the qualitative aspects of risk management by providing relative hazard bands for chemicals being reviewed [OSHA 1998]. Through a consistent and documented process for characterizing chemical hazards according to recommended OEBs, timely and well-informed risk management decisions can be made for chemicals lacking OELs. This process can also be used to prioritize chemicals for which OELs should be established [McKernan and Seaton 2014]. In addition, an occupational exposure banding framework 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 affect health communication, inform implementation of control interventions, and inform medical surveillance decisions. Given these considerations, NIOSH sought to develop and evaluate an occupational exposure banding framework and supporting guidance for use in assessing and characterizing chemical hazards in the workplace. This document provides 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, it is important to distinguish the occupational exposure banding process 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 chemicals with similar hazard profiles. While the occupational hygienists can use 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, essentially link hazards to specific control measures [AIHA 2007; Zalk and Nelson 2008; NIOSH 2009c; Zalk et al. 2010; Beaucham et al. 2012; HSE 2013] (see also http://www.hse.gov.uk/coshh/basics.htm). For this reason the occupational exposure banding process can ultimately be applied for informing risk management and control decisions, but in itself is not control banding, as demonstrated in Figure 1-3.

The control banding approach has utility in the field, but has some limitations. The UK method, for example, provides 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 method was developed to ensure a rigorous scientific foundation that has been evaluated to ensure confidence in the OEB assignments. The development of OEBs require more sophisticated inputs, and thus tends to a more refined output. Additionally, the purpose of OEBs is not to directly link to a control strategy, but rather define a range of exposures to protect worker health. The information provided by OEBs, in concert with exposure assessment, can be used to measure the effectiveness of the controls that are in place, and whether additional controls would be advisable.

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 new chemicals for which no full OEL has been developed. Although use of hazard banding techniques was already well established at the time, an early

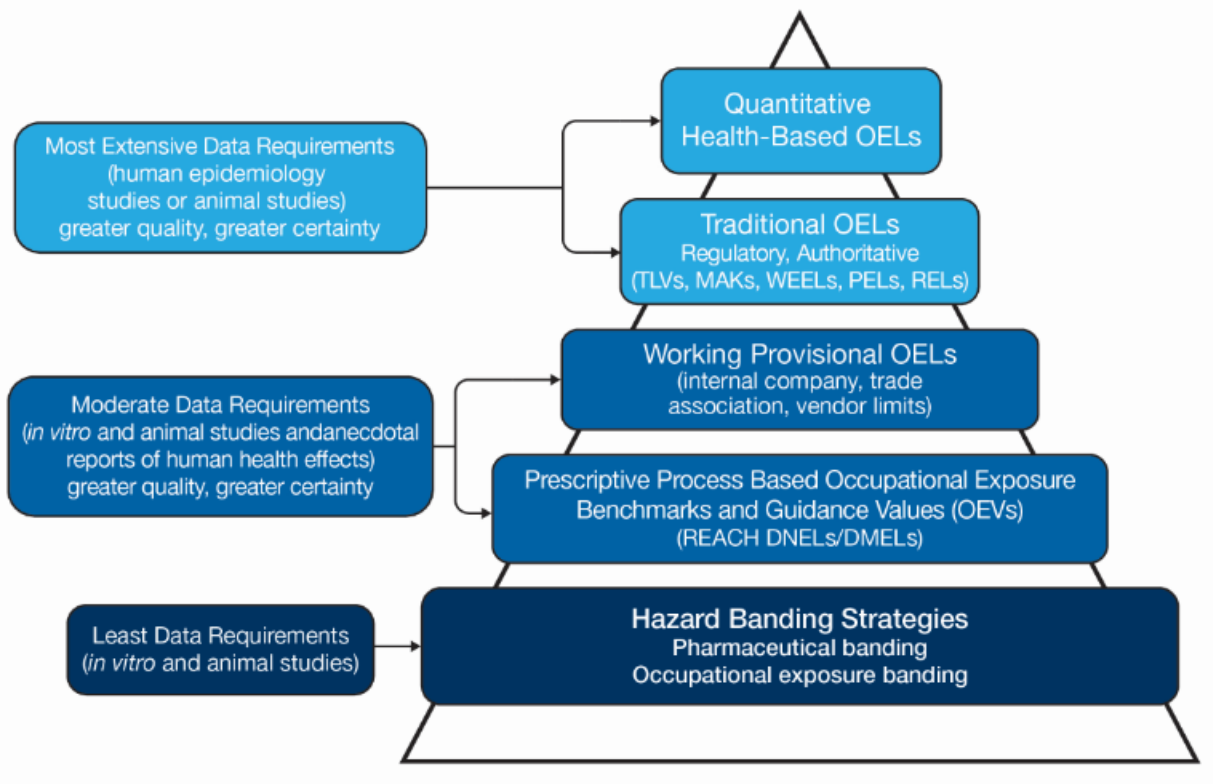
journal publication on the approach highlighted application of "performance-based exposure control limits" in the pharmaceutical sector [Naumann et al. 1996].

The hazard banding technique remains well accepted among the pharmaceutical and larger chemical company risk assessment communities. The development of OEBs, health-hazard categories, hazard groups, and hazard-based exposure control limits indicates a desire within the health and safety community to share information about risk in ways that can be applied more broadly within the occupational hygiene field. The need for this effort is supported by the observation that most chemicals in commerce and thus, encountered in our workplaces, have no published occupational exposure guidelines. This paucity of chemical-specific guidance coupled with the 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 chemicals without OELs, the occupational exposure banding process can be used to (1) array the available hazard data and identify key data gaps, (2) prioritize chemicals 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 call for greater utility of occupational exposure banding has become part of the discussion in the occupational hygiene community [Ripple 2009] and has also been adopted by volunteer OEL setting committees such as the Workplace Environmental Exposure Limits (WEEL®) Committee [Maier 2009]. The OEB concept has also gained emphasis 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 OELs [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 are categorized based on how much toxicological and epidemiological data are required to develop each limit. Quantitative, 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 to form quantitative, health-based OELs are not always available for every potentially hazardous chemical, 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 their data requirements based on when they were assigned and the process used to develop them. Consequently, traditional OELs may be appropriately categorized into several levels of the hierarchy, depending on a number of factors such as data and reporting quality. At the base of the pyramid are health hazard banding strategies, including the NIOSH process to occupational exposure banding. Because the data requirements to determine an OEB are much lower, the precision of the band is also reduced; therefore, occupational exposure banding strategies tend to

result in lower concentration ranges than other processes for developing OELs [Jankovic 2007; Laszcz-Davis et al. 2014; Deveau et al. 2015].

Figure 1-4: Hierarchy of controls. Adapted from [Laszcz-Davis et al. 2014; Jahn et al. 2015].



1.2. Features of the NIOSH Occupational Exposure Bands

The NIOSH occupational exposure banding process shares similar scientific underpinnings with the processes used by many organizations. Key aspects of the process shared by most organizations include:

- 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 air concentration range.

To date, few published processes or resources facilitate harmonization and broader use 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 the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) that identify each relevant hazard independently without providing an overall assessment to guide risk assessment and management. However, NIOSH OEB 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. This process improves the utility of the hazard-based system by providing a target air concentration range that can be used for traditional occupational risk management purposes such as identifying 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 with a similar hazard profile. Because the OEBs are often based on smaller health effects 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

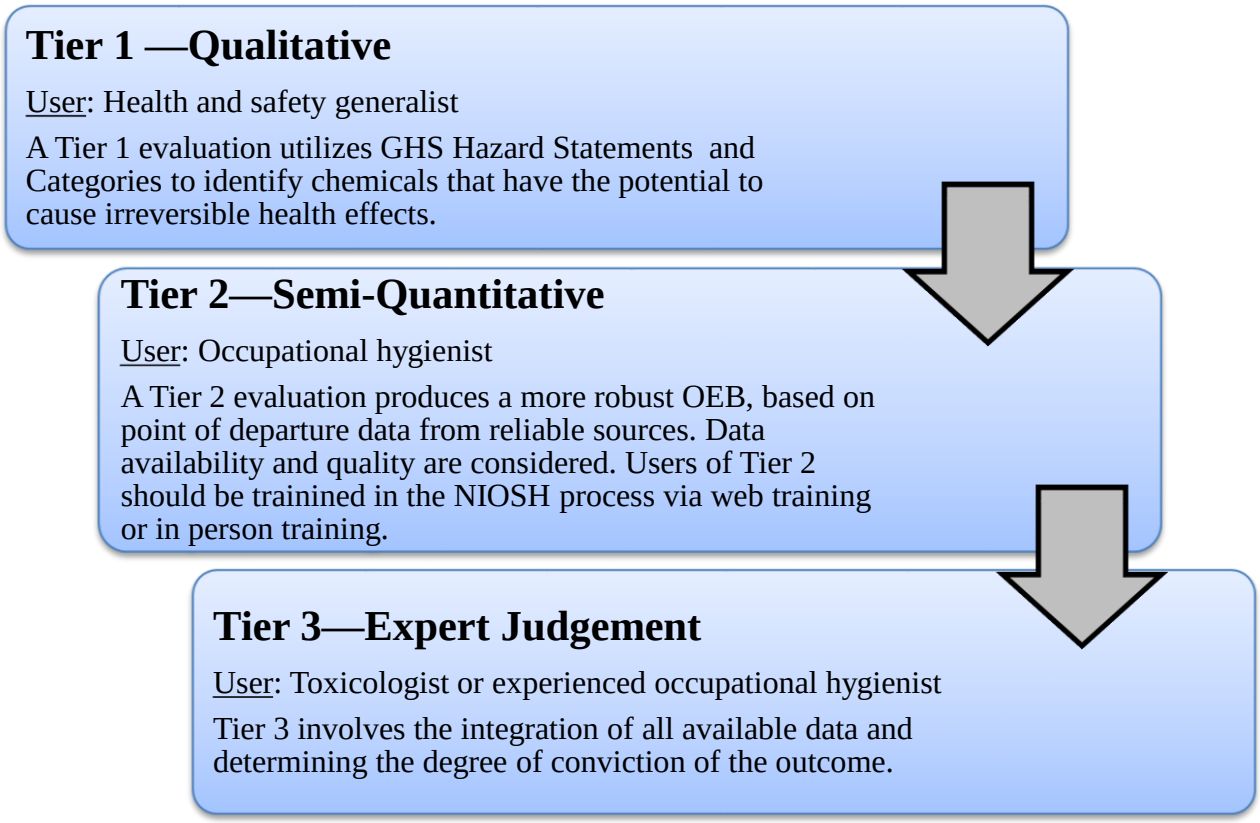
Occupational Exposure Band	Airborne Target Range for Particulate Concentration (mg/m^3)	Airborne Target Range for Gas or Vapor Concentration (ppm)
A	>10mg/m^3	>100 ppm
B	>1 to 10 mg/m^3	>10 to 100 ppm
C	>0.1 to 1 mg/m^3	>1 to10 ppm
D	>0.01 to 0.1 mg/m^3	>0.1 to 1 ppm
E	≤0.01 mg/m^3	≤0.1 ppm

As currently practiced, hazard banding requires a significant amount of technical expertise in industrial 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 (refer to Figure 1-5). The three tiers in the process include the following:

- **Tier 1:** Qualitative OEB assignment based on GHS. Tier 1 involves assigning the OEB based on criteria aligned with specific GHS hazard codes and categories. It is intended for individuals with basic toxicology knowledge. Chemicals with potential for irreversible health effects at relatively low doses warrant assigning band D or band E. Chemicals that are likely to cause reversible health effects are categorized in band C. Bands A and B are not assigned in Tier 1. Since there are relatively low data requirements for Tier 1, there is not enough information to suggest exposure ranges for chemicals Bands A and B in Tier 1. In general, Tier 1 can be used as a quick screening method, but NIOSH recommends going to Tier 2 if the user expertise and data are available.
- **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 chemicals into bands A, B, C, D, or E.
- **Tier 3:** Expert Judgement: OEB based on primary sources and expert judgement: Tier 3 involves the use of expert judgement to assign the OEB based on in-depth review of health effects studies. It should only be performed 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.

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



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 existing data for a chemical 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 database being evaluated. TDS reflects the availability of qualitative and quantitative data for each endpoint. 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 derive a band assignment. This process has the following key uses:

- Documents the data availability for each of the nine potential toxicological or human 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 OEB process has been developed so that it closely aligns with anticipated OELs for chemicals with similar hazard profiles. To build confidence in occupational exposure banding, the alignment between the OEBs and current OELs was evaluated. OEBs assigned to chemicals using the NIOSH methodology are intended to be at least as protective as an OEL assigned to the chemical would be. In this document, an OEB is described as being at least as protective as, or more protective than, the lowest OEL when the concentration range of the OEB includes the OEL or is lower than the OEL. Typically, lower exposures are thought to be more protective of worker health, and thus the word protective is used herein. In a previous study, [Brooke 1998] evaluated the effectiveness of a new UK scheme that utilizes toxicological hazard information to assign chemicals to hazard bands. The UK scheme utilized R-phrases, which were assigned under the European Union (EU) classification scheme, to assign chemicals to one of five toxicological hazard bands (A-E). Like the NIOSH process, each band represents a different target airborne exposure range for dusts and vapors. In the UK study, 111 chemicals were banded using the UK scheme and the target airborne exposure concentration range associated with the hazard band for a specific chemical was compared with the numerical value of the OEL. Results of this study showed that for 98% of the chemicals the target exposure for hazard banding was lower than the OEL.

In this current effort, NIOSH has compared the Tier 1 and Tier 2 banding results for 600 chemicals with existing OELs. 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 5. The overall of Tier 1 bands that were at least as protective as the OEL was 91.5% (combined vapor and particulate).

Chapter 2 : Banding Chemicals with GHS Information: The Tier 1 Occupational Exposure Banding Process

2.0. Technical Approach

The Tier 1 technical criteria use hazard phrases, codes, and categories of the Globally Harmonized System of Classification and Labelling of Chemicals (GHS). GHS covers most hazardous chemicals and provides a uniform approach for communicating hazards related to chemical exposures. Under GHS, chemicals are assigned standardized hazard codes and categories based on their known toxicological characteristics [UNECE 2013]. 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. Since there are relatively low data requirements for Tier 1, there is not enough information to suggest higher exposure ranges for chemicals banded in Tier 1.This cautious approach decreases the likelihood of allowing overexposures. The GHS hazard codes and categories assigned to a chemical 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 hazard codes and categories is found in Section 2.1.

Table 2-1: Tier 1 Criteria Overview: GHS Hazard Codes and Categories for Tier 1 Hazard Banding*

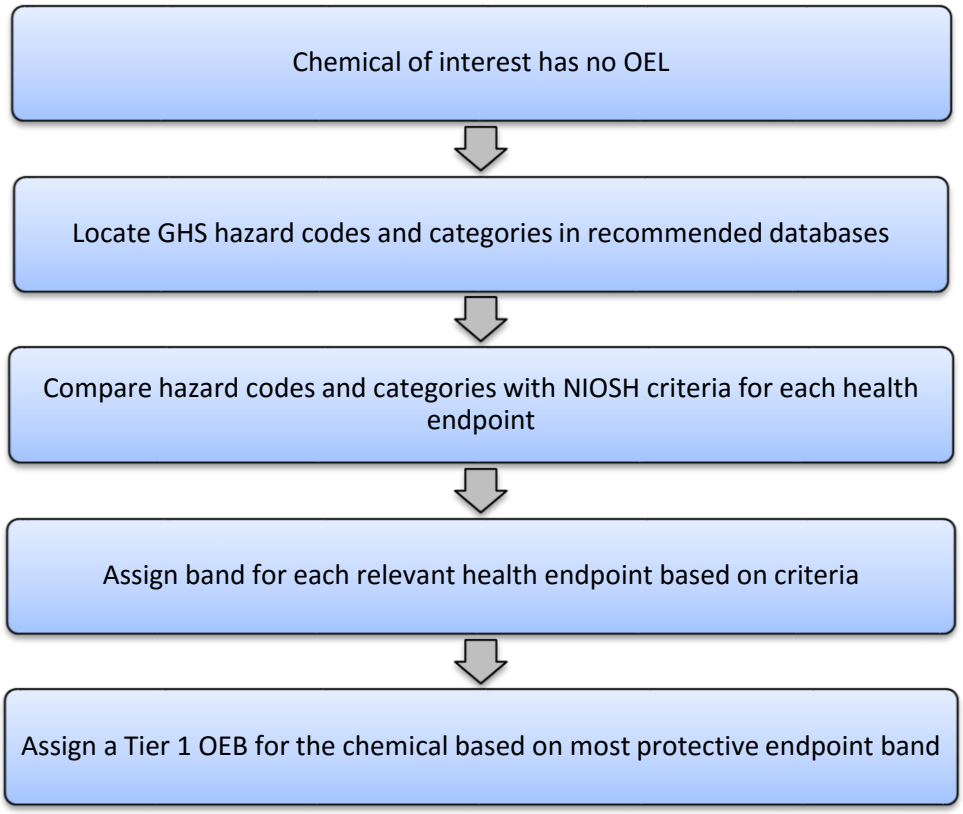
Preliminary NIOSH Tier 1 criteria		C	D	E
OEL ranges	Particle	> 0.1 to ≤ 1 milligrams per cubic meter of air (mg/m^3)	> 0.01 to ≤ 0.1 mg/m^3	≤ 0.01 mg/m^3
	Vapor	> 1 to ≤ 10 parts per million (ppm)	> 0.1 to ≤ 1 ppm	≤ 0.1 ppm
Acute toxicity		H301 Category 3 H302 Category 4	H300 Category 2	H300 Category 1
		H331 Category 3 H332 Category 4	H330 Category 2	H330 Category 1
		H311 Category 3 H312 Category 4	H310 Category 2	H310 Category 1

Skin corrosion/ irritation	H315 Category 2	—	H314 Category 1, 1A, 1B, or 1C
Serious eye damage/ eye irritation	H319 Category 2, 2A or 2B	—	H318 Category 1
Respiratory and skin sensitization	H317 Category 1B (skin)	H317 Category 1 or 1A	—
	—	H334 Category1B	H334 Category 1 or 1A
Genotoxicity	—	H341 Category 2	H340 Category 1, 1A or 1B
Carcinogenicity	—	—	H350 Category 1, 1A, or 1B H351 Category 2
Reproductive Toxicity	H361 *(including H361f, H361d, and H361fd)* Category 2	H360 *(including H360f, H360d, and H360fd)* Category 1B	H360 *(including H360f, H360d, and H360fd)* Category 1 or 1A
Specific target organ toxicity	H371 Category 2 H373 Category 2	—	H370 Category 1 H372 Category 1

**Note that the following hazard codes will not be used for Tier 1 Banding: H200's, H303, H305, H313, H316, H320, H333, H335, H336, H362, and H400's.These H-codes are either not occupationally relevant, or are not sufficient to effect the Tier 1 banding result.*

These codes and categories provide a basis to categorize chemicals based on the severity and reversibility of the health effects. Chemicals 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 protective bands. Chemicals that cause reversible health effects at higher doses, such as skin and eye irritants, are assigned less protective bands, given that the health outcomes are less severe. As shown in the Tier 1 Overview (Figure 2-1), GHS codes are used to discriminate between extremely potent chemicals (assigned to bands D or E) and those for which the criteria suggest a lower level of toxicity. If a chemical has not been evaluated in the GHS system, it cannot be banded in Tier 1. Additionally, chemicals that have been evaluated by GHS, but have not been assigned any 300-level H-codes cannot be banded either. These chemicals require a Tier 2 evaluation for band assignment. In general, Tier 1 can be used as a quick screening method, but NIOSH recommends going to Tier 2 if the user expertise is available. Tier 1 would likely be more be useful when banding a large number of chemicals and deciding which ones should be prioritized for elimination or substitution.

Figure 2-1: Tier 1 overview for quickly banding chemicals in Tier 1.



2.1. GHS Hazard Statements, Codes, and Categories

Hazard statements, codes, and categories are aligned with a standardized hazard criterion for toxicological endpoints defined by GHS. These endpoints are called *hazard classes*. As described in the overview, the health hazard classes as defined by GHS comprise (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 agent. A given chemical may have a hazard statement for any or each of these endpoints, and the statements will vary depending on the severity of the endpoint. For example, a range of GHS health hazard statements address the acute toxicity potentially associated with dermal exposure to a chemical. 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 by GHS is accompanied by an alphanumerical hazard code. Marked by simplicity and ease of use, hazard 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 represented by the code H313 and "Fatal in contact with skin" is coded H310.

Under GHS, chemicals are also assigned a hazard category. A hazard category is the division of criteria within each hazard class. These categories compare hazard severity within a hazard class and are assigned according to specific toxicological cut-points (such as median lethal dose [LD_{50}]) 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 hazard codes, statements, hazard categories is listed in Table A3.1.2 of [UNECE 2013]. As illustrated in Table 2-1 of this document, most of these hazard code and category combinations correspond to a band in the NIOSH occupational exposure banding scheme.

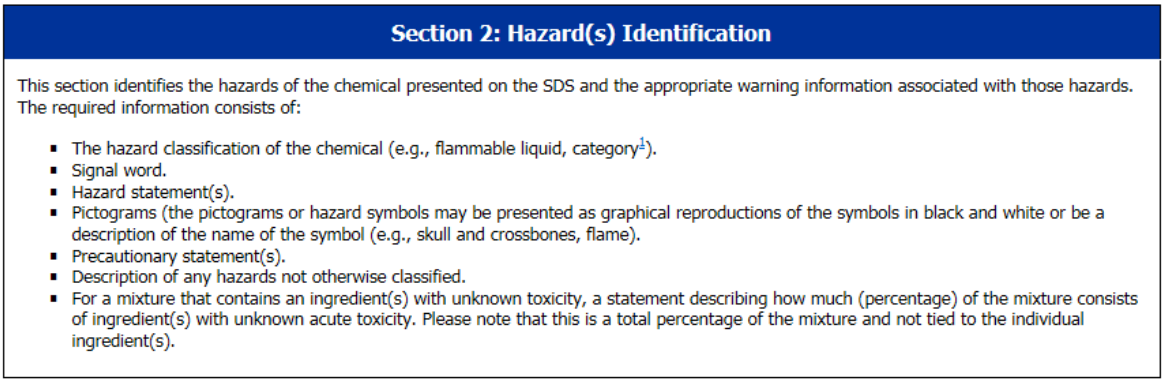
2.2. Data Sources for Hazard Codes and Categories

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

Safety Data Sheets

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 chemicals. 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 will contain GHS hazard statements, codes, and categories that can be used for Tier 1 analysis (Figure 2-2).

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.



Section 2: Hazard(s) Identification

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

- The hazard classification of the chemical (e.g., flammable liquid, category[1]).
- Signal word.
- Hazard statement(s).
- Pictograms (the 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).

Annex VI to the Classification, Labelling and Packaging of substances and mixtures (CLP)

Annex VI is a European database of approximately 1300 chemicals 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 chemicals and mixtures, including GHS hazard statements, codes, and categories can be found in Annex VI.

GESTIS Substance Database

GESTIS is a hazardous chemical database of the German Social Accident Insurance that contains approximately 8000 chemicals [GESTIS 2012]. This website can be found at: http://gestis-en.itrust.de/. Information in GESTIS includes toxicological data, physical and chemical properties, regulations, and hazard statements, codes, and categories.

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 under consideration. Examples include, but are not limited to NIOSH recommended exposure limits (RELs), OSHA permissible exposure limits (PELs), American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit values (TLVs)®, American Industrial Hygiene Association (AIHA) /Occupational Alliance for Risk Science (OARS) workplace environmental exposure limits (WEELs), and European Union (EU) scientific committee on occupational exposure limits. Current OEL information can be found on an OSHA-compliant SDS, in the NIOSH Pocket Guide for Chemical Hazards [NIOSH 2010], or any updates provided by the organization that derived the OEL being considered. If one of these OELs is available, it is not necessary to define an OEB. Controls should be implemented to limit worker exposure to the available OEL. This step is important as it highlights the fact that OEBs are not a replacement to

a traditional OEL, the latter typically having much greater data requirements and more in-depth data evaluation and peer review procedures. However, in the absence of existing government, consensus, or peer-reviewed OELs, occupational exposure banding can be used to make decisions about worker exposure and protection.

In gathering information for Tier 1, the user should identify the hazard codes and categories assigned to the agent. These can be found in the sources listed in Section 1.3 of this document. For hazard banding purposes, majority of the 300-level hazard codes are used, as they correspond to health hazards. Some 300-level codes are not included, as they represent health effects that are not sufficient for Tier 1 banding. The 300-level hazard codes that are not used for banding include: H303, H305, H313, H316, H320, H333, H335, H336, and H362. Furthermore, 200-level hazard codes that correspond to physical hazards and 400-level hazard codes that correspond to ecotoxicology are also not used for banding purposes.

Using the hazard codes assigned to a given chemical for each toxicological endpoint, the technical criteria listed in Table 2-1 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 spreadsheet. Where multiple H-codes for a single chemical are found and those H-codes correspond to different bands, the overall OEB is defined as the most protective band. For example, if Tier 1 H-codes are found that correspond with band D and band E, the chemical 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 protective of these bands is recorded at the bottom of the spreadsheet. This is the Tier 1 OEB for the chemical.

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

Chloral hydrate (302-17-0)

(1) Select a chemical that you are interested in evaluating.
   a. Chloral hydrate (302-17-0)

(2) 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, so proceed to Tier 1 banding.

(3) Determine the three-digit H-codes and hazard categories assigned to the chemical 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 a health hazards. Two hundred-level H-codes correspond to physical hazards, and 400-level 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

(4) Use the Tier 1 criteria overview to determine which OEB corresponds to each of the health based (300-level) H-codes for that chemical. Find the H-code on the chart, and find the corresponding OEB at the top of the column. If no H-code exists for a particular endpoint, 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.

(5) Assign the overall occupational exposure band for the chemical based on the H-code(s) that is/are most protective based on the following rules:
   a. If no H-codes are available for the chemical, do not band in Tier 1. Proceed to Tier 2.
   b. The overall band in a Tier 1 process is never less protective than band C.
   c. If the most protective H-code corresponds to both bands D and E, the hazard categories should be used to make the final determination. If the hazard category is not available, band E should be assigned.

   For chloral hydrate, the most protective H-codes correspond to **band C.**

Table 2-2: Tier 1 Example

Chemical Name: Chloral Hydrate **CAS: 302-17-0**					
Endpoint		**Hazard Code**	**Hazard Category**	**H-code Source**	**Endpoint Band**
Acute Toxicity	**Inhalation**				C
	Oral	H301	Category 3	GHS	
	Dermal				
Skin Corrosion/Irritation		H315	Category 2	GHS	C
Serious Eye Damage/ Eye Irritation		H319	Category 2	GHS	C
Respiratory and Skin Sensitization					
Germ Cell Mutagenicity					
Carcinogenicity					
Reproductive Toxicity					
Specific Target Organ Toxicity					
Most Protective Band					**C**

Chapter 3 : Banding Chemicals beyond GHS: The Tier 2 Occupational Exposure Banding Process

3.0. Overview

The Tier 2 process is recommended by NIOSH whenever data allow because it is more precise than Tier 1and utilizes point of departure data. If the Tier 1 evaluation results in a band E, 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 into a different band. It is most helpful for chemicals for which (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, uncertain, or newer information is available that more clearly reflects the health potency of the chemical.

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. Endpoints evaluated include acute toxicity, skin corrosion and irritation, serious eye damage and irritation, respiratory sensitization, skin sensitization, genotoxicity, carcinogenicity, reproductive/developmental toxicity, and specific target organ toxicity resulting from repeated exposure (STOT-RE).

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 accurate and readily available toxicity data. In the case that 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. Rank 1 and Rank 2 sources are identified in Table 3-2.

The toxicity information for some of the health effects listed above may be categorical in nature (presence/absence of genotoxicity or skin irritation, for example) while other outcomes are expressed through quantitative information and/or potency data. In the latter case, clearly specified quantitative benchmarks, such as median lethal doses (LD_{50}s) for acute toxicity and no-observed-adverse-effect levels (NOAELs), or equivalent point of departure such as benchmark dose lower confidence limit (BMDL), for STOT-RE, are used. Those NOAEL/BMDL values that are used as the basis of agency-derived toxicity benchmarks, such as the reference dose (RfD) from the U.S. Environmental Protection Agency (U.S. EPA) or minimum risk level

(MRL) from the Agency for Toxic Substances and Disease Registry are preferred for assessing chemicals in Tier 2 (Rank 1 or preferred sources), when possible. (Note: The NOAEL/BMDL (or, in some cases lowest observed adverse effect level) 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).

The numerical cut points defining each OEB reflect the spectrum of possible outcomes, from little or no adverse effects (band A) through highly toxic/lethal at low exposures (band E). Earlier, unpublished versions of the Occupational Exposure Banding process included band-specific ranges that approximate the GHS hazard categories, but has refined these cut points based on exposure response analyses, comparisons of OEBs to current OELs, and technical expertise. To ensure the cut points reflect a range of potencies, the fraction of chemicals covered by each occupational exposure band was determined and compared to the potency distribution of a diverse set of chemicals for some endpoints. Additionally, a range of uncertainty factors were considered for deriving OELs that correspond to each band, including interspecies extrapolation, human variability, and severity of effects.

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. 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 end point and a total determinant score (TDS) which is the sum of the scores based on the presence of data for each health endpoint. The TDS is compared to a predetermined threshold for data sufficiency (see Table 3-1). The TDS is an indication of the presence or absence of data. The TDS was developed using professional judgment with consideration of the severity of health outcomes and the likelihood that data regarding a particular endpoint would indicate that the chemical is sufficiently scrutinized to assign a band. It informs the user whether or not there is enough data to make a banding decision.

This document provides an overall strategy for finding the information needed to band a chemical. Additionally, the process for scoring the availability and sufficiency of data for banding in Tier 2 is described. Finally, an electronic web tool and paper worksheets are available for calculating the TDS and determining the OEB.

Table 3-1: Assigned Scores for the Presence of Toxicological Endpoints Encountered in the Tier 2 Evaluation

Toxicological Endpoint	Endpoint Determinant Score (EDS)
Skin Irritation/Corrosion	5
Eye Irritation/Corrosion	5
Skin Sensitization	5
Acute Toxicity/Lethality (LD_{50} or LC_{50})	5
Genotoxicity	5
Respiratory Sensitization	10
Systemic Target Organ Toxicity (STOT-RE)	30
Reproductive and Developmental Toxicity	30
Cancer WOE	20 or 30
Cancer SF, IUR, or TD/TC_{05} (Health Canada)	30
Data Sufficiency/Total Determinant Score (TDS)	30/125

3.1. Overall Strategy for Banding Chemicals in Tier 2

The overall Tier 2 process involves collecting quantitative and qualitative toxicity information on the nine toxicological endpoints using NIOSH-recommended data sources (Table 3-2). These sources have been assigned as Rank 1 (preferred sources) or Rank 2 (secondary 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. In Table 3-3 allows the user to quickly identify which endpoints each source may have data for. Data can be recorded electronically via the NIOSH Occupational Exposure Banding eTool or manually via the worksheets located in Appendix B of this document. Endpoint-specific findings are documented in the spreadsheet, and the OEB 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, the most protective endpoint-specific band is assigned as the OEB. The eTool automatically calculates the TDS, or the TDS can be calculated by the user by adding all of the EDS values together. This process is described in Figure 3-1.

Figure 3-1: Overview of Tier 2 process

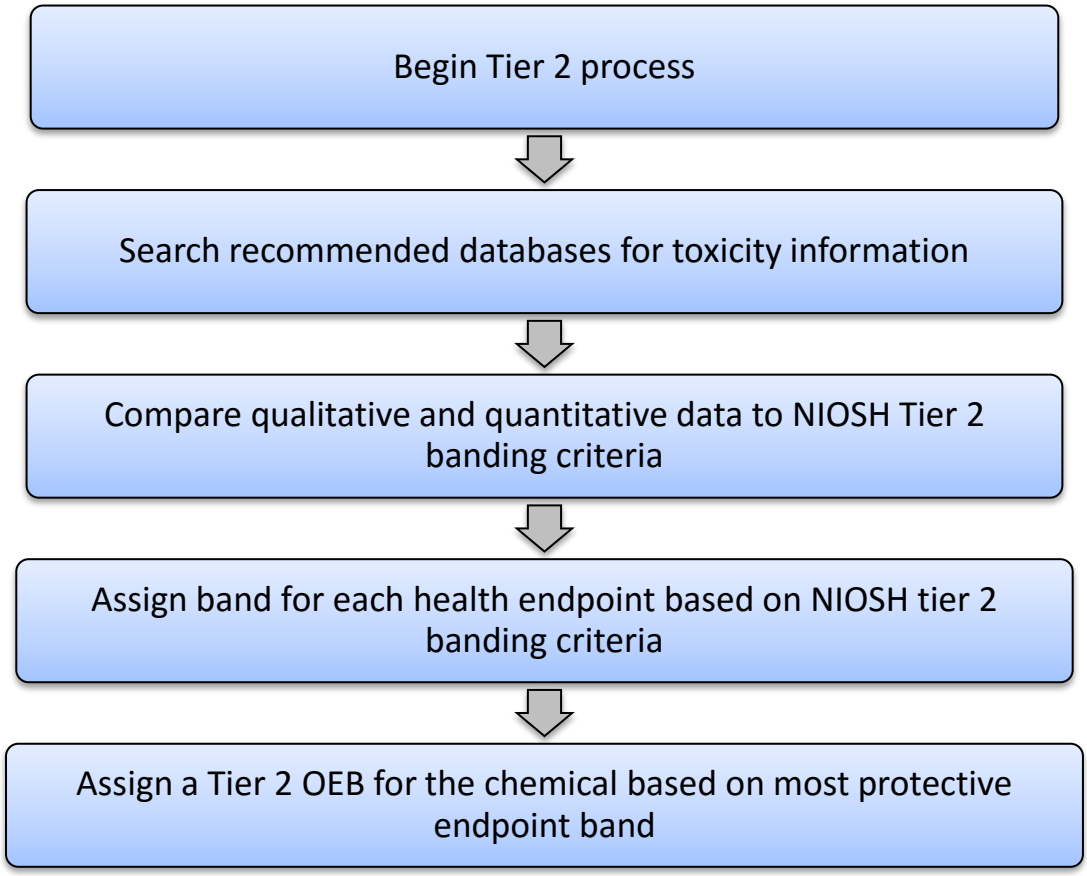


Table 3-2: List of Information Sources for Banding in Tier 2

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 [Canada 1996]	HC
		State of California Office of Environmental Health Hazard Assessment [CAL/EPA 2010]	Cal OEHHA
Reproductive toxicity	1	U.S. National Toxicology Program [NTP 2016]	NTP
		Health Canada [Canada 1996]	HC
		California Environmental Protection Agency [CAL/EPA 2016]	CalEPA
		Agency for Toxic Substances & 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]	U.S. EPA RED
		European Chemicals Agency; Registration, Evaluation, Authorisation and Restriction of Chemicals [ECHA 2016]	ECHA; REACH
Specific Target Organ Toxicity (STOT-RE)	1	Agency for Toxic Substances & 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 [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

Genotoxicity	1	U.S. National Toxicology Program [NTP 2016]	NTP
		Agency for Toxic Substances & 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 & 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
Acute Toxicity	1	National Library of Medicine ChemID Plus [ChemID 2016]	ChemID Plus
		U.S. EPA Superfund Chemical Data Matrix [EPA 2016b]	U.S. 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 & Disease Registry Toxicological Profiles [ATSDR 2016]	ATSDR
Skin Irritation/Skin Corrosion	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
Serious Eye Damage/Eye 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 & 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

Sources	OEB Endpoint								
	Cancer	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
Cal EPA		Rank 1	Rank 1						
OECD		Rank 2	Rank 2		Rank 1	Rank 1		Rank 1	Rank 1
Chem ID plus							Rank 1		
US 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 Hazard Banding in Tier 2: The Total Determinant Score

A compound's TDS is defined as a quantitative measure of data sufficiency for banding in Tier 2 of the evaluation. The TDS is the end product of a scoring system based on the availability of quantitative and/or categorical (semi-quantitative) information on the entire range of toxicological outcomes (determinants).

A Tier 2 evaluation for banding purposes is potentially more discriminating than that based on GHS statements and codes, and could result in a chemical being moved from the band selected in the Tier 1 evaluation. However, 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 represents.

A numerical scheme for data adequacy is used to evaluate chemicals with different combinations of toxicological outcomes and available data.

Technical Approach

Individual scores are assigned to chemicals for the presence of determinant-specific information. The individual score for a given health endpoint is referred to as the endpoint determinant score (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 to a band in Tier 2 with reasonable reliability.

As shown in Table 3-1, different scores are used for the presence of different toxicological outcomes. These EDS values represent weights for the relative importance and severity of the toxicological outcomes under consideration. Thus, the presence of cancer and the existence of quantitative data on systemic toxicological impacts score higher than less severe or life-threatening outcomes, such as eye irritation. Recognizing this disparity, the scheme assigns an EDS of 30 to a chemical for the presence of quantitative data or categorical information on cancer and a score of 30 for systemic toxicity to target organs such as the liver or kidney, etc. In contrast, a score of 5 is assigned for toxicological outcomes that are either less crucial to the overall health of an exposed individual or less reliable as an index of chemical hazard through occupational exposure (for example, acute toxicity).

As shown in Table 3-1, the data sufficiency threshold of 30 (out of a maximum possible TDS of 125) has been selected empirically with the goal of ensuring that at least one of the more health critical endpoints is present for a chemical to be banded in Tier 2. A chemical-specific TDS of less than 30 would indicate that the substance cannot be reliably banded in Tier 2. In such circumstances, a Tier 3 evaluation would be necessary. A TDS of 30 or more would justify

choosing the most stringent band from all of the determinants evaluated as the Tier 2 outcome. If this differs from the outcome of the Tier 1 evaluation, it would then be justifiable to band the chemical to either a less or more health protective band than that obtained in Tier 1. The minimum TDS criteria are waived if any of the endpoint bands are E. In this case, the chemical 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 overreliance on a particular determinant for banding where several data points may be available within a specific toxicological category. Thus, if a number of indices of acute toxicity are available (LD_{50}, LC_{50}) for a particular chemical, simplistically, these might unbalance the evaluation by resulting in an EDS of 10. However, using the EDS concept, the presence of any or all of these determinants would still result in an EDS of 5. The Tier 2 checklist shows how this information should be recorded (see highlighted cells in Table 3-4).

Special TDS considerations for Cancer Data

If quantitative cancer information for a chemical is available, it will take precedence over qualitative or categorical data. An EDS of 30 is assigned for any type of quantitative data described in the NIOSH criteria (e.g. SF, TD_{05}, TC_{05}, etc.). In the absence of quantitative data, categorical data is used. An EDS of 20 is assigned for the presence of categorical data, **except** when the categorical data results in a band E. In the latter case, an EDS of 30 is assigned.

Table 3-4: Checklist for Tier 2 Hazard Banding

Chemical Name: **CAS:**			
Endpoint	**Data**	**EDS**	**Endpoint Band**
Acute Toxicity	Source:		
Skin Corrosion/Irritation	Source:		
Serious Eye Damage/ Eye Irritation	Source:		
Respiratory Sensitization	Source:		
Skin Sensitization	Source:		
Genotoxicity	Source:		
Carcinogenicity	Source:		
Reproductive Toxicity	Source:		
Specific Target Organ Toxicity	Source:		
OVERALL Tier 2 BAND		**TDS=**	

3.3. Banding Potentially Hazardous Chemicals on the Basis of Carcinogenicity

Cancer is a group of diseases that cause 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 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, chemicals 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. Chemicals 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)." [UNECE 2013]

Evidence of an agent'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 for carcinogenicity can be found in Table 3-5.

Table 3-5: 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, the banding resulting from the quantitative assessment takes precedence. Recommended sources for information about carcinogenicity are listed in Table 3-5.

Quantitative Assessment – Carcinogenicity

The quantitative assessment of carcinogenicity uses a measure of potency as a more accurate way to band chemicals than a purely qualitative approach. Because OEBs represent concentration ranges, potency information is more valuable in terms of selecting the appropriate band. Potency data, when available, 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 shown in Table 3-6.

Table 3-6: Criteria for Carcinogenicity Toxicity (Quantitative Analysis)

NIOSH Banding Criteria for **Cancer**			
Exposure/ Dosing Route	**Endpoint Band**		
	C	**D**	**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	$< 3 \times 10^{-6}$ (µg/m^3)$^{-1}$	$\geq 3 \times 10^{-6}$ 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}	> 16700 µg/m^3	> 5 to ≤ 16700 µg/m^3	≤ 5 µg/m^3

Three sources, U.S. EPA IRIS, Health Canada, and State of California Office of Environmental Health Hazard Assessment Cal-OEHHA, have sufficient quantitative information to refine the carcinogenicity hazard band and should be used for quantitative assessment. Once a band has been selected based on a potency estimate, there is no need to go on to the next source for this analysis.

Endpoint-Specific Band Selection – Quantitative Carcinogenicity

- To band a chemical 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 3-6). 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 protective band takes precedence for band selection in Tier 2. The most protective SF and IUR values are the highest, rather than the lowest values, as these values represent the proportion of a population at risk for developing cancer.
- If a TD_{05} is available for the agent, ensure that the units are mg/kg-day.
- If a TC_{05} is available for the agent, ensure that the units are µg/m^3.
- If quantitative carcinogenicity data are available, assign a EDS of 30 points.

Qualitative Assessment – Carcinogenicity

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

Table 3-7: 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 Report on Carcinogens (RoC) can be searched for the chemical of interest. If NTP has classified the chemical 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. In this case, the EDS is 0. No band is assigned, and the next source is assessed.

Environmental Protection Agency Integrated Risk Information System

- The U.S. EPA IRIS carcinogen classification can be checked on the U.S. EPA IRIS website. The weight of evidence (WOE) descriptor should be evaluated.
- If the WOE descriptor is:
    - *Group A (human carcinogen), Carcinogenic to humans, Group B1 (probable human carcinogen), Likely to be carcinogenic to humans* or *Group B2 (probable human carcinogen),* assign a determinant score of 30 and band E.
    - *Group C (possible human carcinogen* or *suggestive evidence of carcinogenic potential),* assign a determinant score of 20 and band D. For this group, U.S. EPA found some evidence of carcinogenicity but the data were not sufficiently robust to have high confidence in the assessment.
    - *Group D (not classifiable as to human carcinogenicity* or *data are inadequate for an assessment of carcinogenic potential),* a determinant score of 0 is assigned. No band is assigned based on this source. For this group, the EPA did not find enough information to assess the carcinogenicity of the chemical.
    - *Group E (evidence of non-carcinogenicity for humans* or *not likely to be carcinogenic to humans),* assign a determinant score of 30 and endpoint band A. For this group, EPA found that the data were sufficiently robust to conclude that the chemical is not likely a human carcinogen.

International Agency for Research on Cancer

- The IARC carcinogen classification can be found on the IARC Monograph website (Table 3-5). Check the corresponding IARC monograph website for any additional information. If IARC has classified the chemical as
    - Group 1 (carcinogenic to humans), Group 2A (probably carcinogenic to humans) or Group 2B (possibly carcinogenic to humans), assign a determinant score of 30 and a preliminary endpoint band E.
    - *Group 3 (not classifiable as to its carcinogenicity to humans)* or IARC has not classified the chemical at all, move to the next source. No score is assigned.
    - *Group 4 (probably not carcinogenic to humans),* assign a determinant score of 30 and endpoint band A.

State of California Office of Environmental Health Hazard Assessment

- CalOEHHA lists chemicals known to cause cancer as part of its Proposition 65 list. The list is available online and can be searched by name or CAS number? If the chemical has the designation "cancer" under the heading *Type of Toxicity,* 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, CalEPA, 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 Chemicals based on Reproductive Toxicity

Reproductive toxicity includes adverse effects on reproductive health in adults and developmental toxicity in offspring. 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, and 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 compound-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.

Reproductive toxicity includes "adverse effects on sexual function and fertility in adult males and females, as well as developmental toxicity in the offspring" [UNECE 2013].

Data Sources – Reproductive Toxicity

Sources for Tier 2 information for reproductive toxicity can be found in

Table 3-8. Standard animal studies in rats and other experimental animals provide relevant data for banding chemicals according to reproductive toxicity. In assigning a band for these effects, NOAELs/BMDLs that are specified in reviews of studies featuring oral, dermal, and inhalation exposures in experimental animals are aligned to the quantitative technical criteria listed in Table 3-9, with emphasis on those studies conducted using internationally accepted protocols (i.e., OECD and U.S. EPA Test Guidelines).

Table 3-8: Sources of Information 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 & 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	U.S. EPA RED
		European Chemicals Agency; Registration, Evaluation, Authorisation and Restriction of Chemicals	ECHA; REACH

Classification Criteria – Reproductive Toxicity

For a Tier 2 assessment, human or animal data are needed for assigning a band that reflects the reproductive toxicity potential of a chemical. NIOSH recommends occupational exposure banding assignments for reproductive toxicity based on NOAELs/BMDLs (Table 3-9). This dose-response information provides the quantitative basis for assigning a band for this endpoint. NOAELs/BMDLs are generally available from reviews conducted by governmental, national, international, and professional agencies. The dose-response information provides the quantitative basis for assigning the band for this endpoint.

NOAEL and BMDL values should be derived from studies that use internationally accepted test methods, such as the OECD Guidelines for the Testing of Chemicals and EPA Good Laboratory Practices (GLP) that assess:

(1) Developmental toxicity
(2) Perinatal and postnatal toxicity
(3) One-generation or two-generation toxicity
(4) Reproductive/developmental toxicity
(5) Combined repeated dose toxicity study 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 3-9: Criteria for Reproductive Toxicity Endpoint

NIOSH Banding Criteria for **Reproductive Toxicity** (NOAEL/BMDL/BMCL)					
Exposure/ Dosing Route	**Endpoint Band**				
	A	**B**	**C**	**D**	**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 and vapors)	> 10,000 ppm	> 1,000 to ≤10,000 ppm	> 100 to ≤1,000 ppm	> 10 to ≤100 ppm	≤10 ppm
Inhalation (dusts and mists)	> 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

Approach to Data Selection – Reproductive Toxicity

Recommended sources are consulted for relevant NOAELs/BMDLs and, when these are not available, the LOAEL for the reproductive toxicity endpoint (see Table 3-8 for data sources). The following approach is suggested.

Endpoint-Specific Band Selection – Reproductive Toxicity

The following steps are suggested to assign a band:

(1) If route-specific NOAELs/BMDLs are available, use them directly to assign a band.
(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.
(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.
(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.

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 experimental 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. This score is assigned 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 [Jarabek et al. 1994] provides a detailed explanation of how the tenets of the ideal gas law can be used to convert concentrations of gases and vapors expressed in ppm to mg/m^3 and vice versa.

At 25°C and 760 mm Hg 1 g-mole of a perfect gas or vapor occupies 24.45 L; under these conditions, the conversion becomes:

$$mg/m^3 = (ppm \times MW)/24.45$$

Converting concentrations expressed in mg/m^3 to ppm would require inverting the above calculation as follows:

$$ppm = (mg/m^3 \times 24.45)/MW$$

3.5. Banding Potentially Hazardous Chemicals on the Basis of Specific Target Organ Toxicity (STOT-RE)

Specific Target Organ Toxicity following Repeated Exposure (STOT-RE) 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 has produced serious changes to the biochemistry or hematology of the organism and these changes are relevant to human health" [UNECE 2013].

Examples of toxicological endpoints applicable to the STOT-RE hazard banding category include (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 can be found in Table 3-10.

Table 3-10: Criteria for Specific Target Organ Toxicity (STOT-RE) Endpoint

ENDPOINT	Rank	SOURCE OF INFORMATION	ACRONYM
Specific Target Organ Toxicity (STOT-RE)	1	Agency for Toxic Substances & 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. These data are generally available from authoritative reviews conducted by governmental, national, international and professional agencies throughout the world. These agencies have published reference doses or concentrations (RfDs and RfCs), minimal risk levels

(MRLs), acceptable daily intakes, tolerable daily intakes or concentrations (TDIs or TDCs), tolerable intakes (TIs) or tolerable concentrations (TC), etc. These values are based on target organ toxicity information and criteria specific to the organization that developed them. These reference doses/concentrations are derived based on NOAELs/BMDLs or LOAELs (when NOAELs 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), 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 recommends criteria for each of the occupational exposure bands as listed in Table 3-11. The criteria refer to dose/concentrations from standard 90-day toxicity studies conducted in rats. However, availability of a reliable NOAEL/BMDL from a repeat dose study of adequate quality in another animal model would be acceptable to assign a STOT-RE band to a chemical. Similarly, a NOAEL/BMDL from a study of less than 90 days duration (but at least 28 days or) would be applicable for banding according to this endpoint, if a suitable conversion factor is applied to account for the shorter duration.

Table 3-11: Criteria for Specific Target Organ Toxicity (STOT-RE) Endpoint

NIOSH Banding Criteria for **Specific Target Organ Toxicity** (NOAEL/BMDL)					
Exposure/ Dosing Route	**Endpoint Band**				
	A	**B**	**C**	**D**	**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 (dusts and mists)	>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 and vapors)	>30,000 ppm	>3,000 to ≤30,000 ppm	>300 to ≤3,000 ppm	>30 to ≤300 ppm	≤30 ppm

** Multiple NOAELs/BMDLs for one chemical may be available. The point of departure 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 derived target organ toxicity benchmark values are available from Rank1 sources (Table 2.8), identify, for each route, the single NOAEL/BMDL that is the most health-protective and enter the value(s) in the appropriate section of the chemical-specific eTool or paper worksheets. The applicable NOAEL/BMDL is compared to the NIOSH criteria (Table 3-11).and the most stringent band is assigned as the endpoint band for the chemical.

In the absence of Rank 1 data, there are other sources of STOT-RE information (e.g., authoritative compilation of studies such as SIDS, 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 primary source of evidence for this hazard class and the associated bands, but standard animal studies in rats and other experimental animals that provide this information are 28-day, 90-day, or lifetime studies (up to 2 years). Because human data are not readily available, NOAELs/BMDLs are identified in experimental animals following oral, dermal, and inhalation exposures.

Several adjustments may be needed before using data to assign a band. Depending on study design, a duration-adjustment may be necessary. If 90-day or longer duration NOAELs/BMDLs are available, these values are used directly to assign a band for a chemical. If a NOAEL/BMDL is from a 28-day but less than 90-day exposure, this should be divided by a factor of three to derive a NOAEL/BMDL equivalent to a 90-day exposure. The resulting value is used to assign a band.

Another adjustment that may be required is a LOAEL-to-NOAEL adjustment. If a LOAEL rather than a NOAEL is available, the LOAEL is divided by 10 to convert the LOAEL to a NOAEL equivalent.

If multiple NOAELs/BMDLs are available for any route of exposure, the lowest value is used for that route. When NOAELs are available for each route and route-specific bands are assigned, the overall STOT-RE band is represented by the most health-protective band (the most stringent). If no route-specific NOAELs are available, criteria for the STOT-RE endpoint are not met and no STOT-RE specific band will be assigned for this chemical.

Endpoint Determinant Score – STOT-RE

The NOAEL/BMDL that serves as the basis for the safe dose/concentration provided in authoritative reviews can be based on (1) quantitative epidemiological information on STOT-RE endpoint 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 a chemical in Tier 2.

3.6. Banding Potentially Hazardous Chemicals on the Basis of Genotoxicity

The genotoxicity health endpoint is related to changes in genetic material. While genotoxicity and germ cell mutagenicity are similar terms, it is important to draw the distinction. Germ cell mutagens are chemicals 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, while genotoxicity is a more general term that includes mutations and other DNA or chromosome level changes. Thus, genotoxicity, by definition, includes mutagenicity. Chemicals can be classified as to genotoxicity from a range of in vivo and in vitro tests [UNECE 2013].

Agents with demonstrable genotoxic properties have been subdivided into categories according to the available evidence. For example, chemicals for which positive evidence exists from human epidemiological studies may be regarded as agents *known* to be genotoxic.

In practice, data for few if any genotoxic chemicals rise to this level of certainty, and results from a variety of alternative assays must be considered (see Table 3-12). 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 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.

Table 3-12: Examples of Genotoxicity Tests Applicable to the Tier 2 Hazard 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 2013].

Approach to Data Selection – Genotoxicity

For Tier 2 assessments, the preference is to rely on the overall judgment on genotoxicity provided from an authoritative Rank 1 or Rank 2 source (Table 3-13). Relevant information on all of these tests can be found in authoritative reviews and summaries, as listed below. For ease of access, agent-specific 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 chemicals according to this criterion involves searching for chemical-specific data from a range of genotoxicity tests.

Data Sources – Genotoxicity

Sources for Tier 2 information for Genotoxicity can be found in Table 3-13.

Table 3-13: Sources for Genotoxicity Endpoint

ENDPOINT	Rank	SOURCE OF INFORMATION	ACRONYM
Genotoxicity	1	U.S. National Toxicology Program	NTP
		Agency for Toxic Substances & 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

Endpoint-Specific Band Selection - Genotoxicity

The totality of the evidence of genotoxicity, as provided by summaries and or tabulated data in authoritative reviews, should be entered by source in the spreadsheet. If there was no record for a particular compound enter “no source info.” If there was a record, but no genotoxicity information enter “no data” for that particular source. If information was found, enter positive or negative in the appropriate row for that source, depending on the preponderance of the evidence.

For the checklist, choose the band that is most appropriate based on the summary statements in authoritative reviews or evaluation of the data. As shown in Table 3-14, the following bands 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 from in vivo assays and mammalian assays supported by in vitro and non-mammalian 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 3-12)

If there are no studies for genotoxicity, enter "no data" into the spreadsheet. The determinant score when appropriate data are available is 5 for genotoxicity. Leave blank if there are no data.

Table 3-14: Criteria for Genotoxicity Endpoint

NIOSH Banding Criteria for **Genotoxicity**		
Endpoint Band		
A	**C**	**E**
Negative Results	Mixed results	Positive Results

Endpoint Determinant Score – Genotoxicity

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

3.7. Banding Potentially Hazardous Chemicals 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 2013]. This chapter discusses respiratory sensitization.

In Tier 2, respiratory sensitizers are allocated bands using qualitative data. If epidemiological or clinical dose-response data are available for respiratory sensitization, 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 can be found in Table 3-15.

Table 3-15: Data 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
	2	Agency for Toxic Substances & 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 3-15.

Respiratory sensitization or respiratory allergy refers to an allergic reaction in the respiratory tract (e.g., asthma) following exposure to the chemical. Respiratory sensitization does not refer to irritation or damage to pulmonary tissue following chemical exposure. These outcomes would be considered for banding under specific target organ toxicity after repeated or prolonged exposure. Acute or single exposure respiratory irritation is not used in the OEB protocol. According to the OSHA HCS, "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 upon 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, regulatory 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 2013] has proposed no 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 3-16. Given the imprecise nature of the cut-points for banding this endpoint, some latitude is available for persons to use a qualitative approach, on the basis of the total evidence.

Table 3-16: Criteria for Respiratory Sensitization Endpoint

NIOSH Banding Criteria for **Respiratory Sensitization**		
Endpoint Band		
A	**C**	**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 currently exist from which a reliable point of departure can be identified, inferential evidence on a chemical's potential to induce this response can be drawn from conclusions provided in reviews from recommended databases (e.g., ATSDR, IRIS, REACH assessments, OECD SIDS, etc.)

Endpoint-Specific Band Selection – Respiratory Sensitization

The following steps are followed to assign a band:

(1) Assign band E, if the classification system indicates the substance is a respiratory sensitizer.
(2) Assign band C, if results from these sources are mixed or the evidence is determined to be inconclusive.
(3) Assign band A if the classification system or evidence indicates the substance is not a respiratory sensitizer.

3.8. Banding Potentially Hazardous Chemicals on the Basis of Skin Sensitization

In addition to respiratory sensitization, the banding process evaluates a chemicals potential to cause skin sensitization. A *skin sensitizer* is "a substance that will lead to an allergic response following skin contact" [UNECE 2013].

In Tier 2, skin sensitizers are assigned to one of five endpoint bands, ranging from band E (extreme sensitizers) to band A (non-sensitizers), 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 can be found in Table 3-17.

Table 3-17: Data 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. Skin sensitization does not refer to irritation and corrosion to skin following chemical 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 HCS, "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 local lymph node assay, the guinea pig maximization test, and the Buehler assay.

NIOSH has partially established its sensitization banding criteria on GHS. GHS has proposed specific 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 guinea pig maximization

test and 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 2013]. 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 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 3-18. In the case that both qualitative and quantitative data exist for this endpoint, each should be surveyed against the NIOSH skin sensitization criteria, and whichever data provide the most health protective band should be used. The NIOSH skin notation assignment can also be used to assign a band for skin sensitization as indicated in Table 3-18.

If LLNA EC3 values are available, the chemical is assigned one of five potency categories (A–E) on the basis of their 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 test, based on 2012 European Chemical Agency recommendations.

Table 3-18: Criteria for Skin Sensitization Endpoint

NIOSH Banding Criteria for **Skin Sensitization**			
Test Type	**Endpoint Band**		
	A	**C**	**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
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

Approach to Data Selection – Skin Sensitization

Band the chemical based on the LLNA EC3 value or the incidence data for skin sensitization. Select the most health-protective band as the final band. When quantitative skin sensitization data are available from more than one assay, select the band that is most health-protective.

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 the most desirable source of evidence for this hazard class and the associated bands, skin sensitization band selection can use data from standard animal studies in mice (LLNA) and guinea pigs (Buehler test) from authoritative organizations.

The following steps are followed to assign a band:

(1) Consult authoritative reviews (Table 3-17) to identify reliable LLNA EC3 or sensitization incidence data reported in Buehler guinea pig test for a chemical. For banding purposes, these are compared to the technical criteria set forth in Table 3-18.

(2)Assign a band based on mouse LLNA EC3 value and/or Buehler test incidence data for sensitization.

(3) If multiple LLNA EC3 values and/or incidence data for sensitization from Buehler test are available, the most health-protective value or incidence data is used.

(4) 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 according to Table 3-17.

Endpoint Determinant Score – Respiratory and Skin Sensitization

The availability of data to support conclusions provided in authoritative reviews can be based on observational information in humans or experimental data in animals on respiratory sensitization. If appropriate data for banding are available, this contributes an EDS of 10 in the overall assessment of whether sufficient information is available for banding a chemical in Tier 2. The availability of data on skin sensitization contributes an EDS of 5 in the overall assessment of whether sufficient information is available for banding a chemical in Tier 2. These scores are assigned on the availability of the information, regardless of the outcome of the test or observation (positive/negative).

3.9. Banding Potentially Hazardous Chemicals on the Basis of Acute Toxicity

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]

When acute toxicity data are used for hazard banding, chemicals 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 can be found in Table 3-19.

Table 3-19: Data 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	U.S. 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 & Disease Registry	ATSDR

Classification Criteria for the Bands – Acute Toxicity

The banding scheme uses five categories (A to E) in which band E is the most precautionary. The numerical criteria (cut-points) for the LD_{50}s and 4-hour LC_{50}s are given in Table 3-20.

Approach to Data Selection – Acute Toxicity

Banding a chemical for acute toxicity in Tier 2 involves searching through NIOSH-recommended literature sources listed in Table 3-19 and recording all available LD_{50} and LC_{50} values for the chemical. A spreadsheet is provided for this purpose in Appendix B. The lowest (most health-protective) value by exposure route is used to determine the appropriate band according to the LD_{50}/LC_{50} technical criteria shown in Table 3-20. This determination is then entered into the Tier 2 checklist in the appropriate row and column.

A determinant score of 5 is entered if any acceptable acute lethality data are available for the chemical in question. If more than one type of acute lethality data are available for a chemical under investigation, for example, an oral LD_{50} *and* an inhalation LC_{50}, the acute toxicity determinant score remains at 5.

Table 3-20: Criteria for the Acute Toxicity Endpoint

NIOSH banding criteria for **Acute Toxicity**					
Exposure/Dosing Route	**Endpoint Band**				
	A	**B**	**C**	**D**	**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 (LC_{50})	> 20,000 ppmV/4h	>2,500 to ≤ 20,000 ppmV/4h	>500 to ≤ 2,500 ppmV/4h	>100 to ≤ 500 ppmV/4h	≤ 100 ppmV/4h
Inhalation vapors (LC_{50})	> 20.0 mg/liter/4h	>10.0 to ≤ 20.0 mg/liter/4h	>2.0 to ≤ 10.0 mg/liter/4h	>0.5 to ≤ 2.0 mg/liter/4h	≤ 0.5 mg/liter/4h
Inhalation dusts and mists (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

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

Acute toxicity data may be available from a variety of different types of studies, some of which may be more reliable and relevant to banding than others. Not all acute toxicity 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, guinea pigs, etc. should be employed for banding. Values from species that are less likely to be adequate models for toxicity in humans (such as chicken, frog, etc.) should not be used for banding.
- Studies where the administration of the chemical dose was other than oral, dermal, or inhalation (e.g., subcutaneous, intraperitoneal, intravascular) should be rejected and not used for banding.

Other conditions requiring rejection for banding purposes include:

- Studies where the experimental animal is not stated
- Studies where the experimental animal is described as "mammal(s)"
- Lethality data that do not reflect the median lethal dose, such as LD_{10}, or LD_{LO}, etc.
- 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 male and female (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). In that case, 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, the LC50 should be converted to a 4-hour equivalent. While Haber's rule (simple proportionality) is sometimes used for these types of conversions, NIOSH recommends using the ten Berge equation:

$$Adjusted\ LC50\ (4\ \text{hours}) = LC50(t) \times ((t/4)^{(1/n)})$$

Where: LC50 (t) = LC50 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]. A default value of 1 is used for "n" when extrapolating to longer durations and a default value of 3 is used for "n" when extrapolating to shorter durations.

Table 3-21 gives (1) a list of adjustment factors, (2) the resulting 4-hour LC_{50} calculated for an experimentally derived value of 100 mg/m^3 for the different exposure periods, and (3) the comparable 4-hour LC_{50} values determined through the simple application of simple proportionality (Haber's rule). This adjustment table is not specific to the physical form of the chemical, and can be applied for particles and vapors/gases.

Table 3-21: Duration Adjustment Factors for Acute Toxicity

Exposure duration (hours)	ten Berge constant	Adjustment factor	Derived 4-hour LC_{50}	Comparable 4-hour LC_{50}s by Haber's rule
1	1	0.25	25	25
2	1	0.5	50	50
3	1	0.75	75	70
4	1	1	100	100
5	3	1.08	108	125
6	3	1.14	114	150
7	3	1.2	120	175
8	3	1.26	126	200
9	3	1.31	131	225
10	3	1.36	136	250

As shown in Table 3-21, for exposures longer than 4 hours, the derived 4-hour LC_{50} values are lower, and thus more health-protective than those calculated using Haber's rule. It is conceivable that this difference may affect band selection for some chemicals.

After making appropriate conversions, the user should enter the values in the appropriate units (ppm/4 hours or milligrams per liter of air/4 hours) according to whether the agent is a gas, vapor, or dust/mist. For banding purposes, the appropriate cut-points for LC_{50} values associated with agents in different physical forms are given in Table 3-20. An explanatory note with applicable definitions is given in the Addendum.

Endpoint-Specific Band Selection – Acute Toxicity

When all the acceptable LD50 and LC50 data have been assembled by data source for each route (oral, dermal, inhalation), the lowest value will be compared to the technical criteria for band selection. The spreadsheet enters the selected band in the column headed Endpoint-specific band selection (right-hand side) based on the most stringent band among all the routes with acceptable LD50 or LC50 values.

Endpoint Determinant Score – Acute Toxicity

If at least one acceptable data point is available, a score of 5 is assigned to the endpoint determinant score. The presence of multiple acceptable data points also warrants a score of 5. If there are no available values for a particular acute toxicity/lethality endpoint, no band is assigned for acute toxicity and a determinant score of 0 is assigned.

3.10. Banding Potentially Hazardous Chemicals on the Basis of Skin Corrosion and 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." 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 2013].Direct effects on the skin can be defined as nonimmune mediated (non-allergic) 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 great susceptibility of the skin to toxic exposures. Many direct skin effects can affect the skin barrier integrity resulting in an increased potential of chemical penetration and subsequent risk of systemic toxicity [NIOSH 2009b]. Direct effects on the skin beyond irritation/corrosion are not defined or included in the GHS decision process. Despite their absence from GHS, these effects may have substantial adverse effects on the lives and health of workers. In-depth descriptions of these health endpoints, in addition to supplemental information useful for hazard characterization purposes of such direct skin effects beyond irritation and corrosion, are available in the NIOSH Current Intelligence Bulletin Number 61 [NIOSH 2009b].

Data Sources – Skin Corrosion/Irritation

Sources for Tier 2 information for skin corrosion/irritation can be found in Table 3-22.

Table 3-22: Data 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 & 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 throughout the world as listed in Table 3-22. GHS [UNECE 2013] has proposed criteria for Categories 1 and 2, but not Category 3, skin corrosion/irritation substances. NIOSH has not recommended band assignments on the basis of potency information (e.g., dose-response data, Draize scores) for skin corrosion/irritation substances under Tier 2 assessments. Where dose-response data are available for irritation or other direct effects, such data may be used as part of the STOT endpoint. The recommended NIOSH criteria shown in Table 3-23 assigns bands for skin corrosion/irritation based on classification systems from authoritative organizations.

Table 3-23: Criteria for Skin Corrosion/Irritation Endpoint

NIOSH Banding Criteria for **Skin Irritation/Skin Corrosion**			
Endpoint Band			
A	**B**	**C**	**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

Approach to Data Selection – Skin Corrosion/Irritation

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 strategy)[NIOSH 2009b]
- 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 multiple classifications or conclusions by various authoritative reviews are present, the most health-protective 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 non-concentrated material. For example, a strong acid such as hydrochloric acid banded using this process would be classified as band E for the Skin corrosion/irritation endpoint, even though non-concentrated dilutions can be non-irritating.

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 3-23, the findings based on classification systems provided by authoritative organizations or conclusions provided in authoritative reviews (Table 3-22).

For skin irritation or corrosion, 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 causes irritation include qualitative descriptions that suggest that the chemical 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 based on the severity of the reaction. Reversible, mild effects that occur at high concentrations should be placed into bands B and C, while serious, irreversible effects that occur at low concentrations are banded in bands D and E.

For direct effects on the skin other than skin irritation/corrosion, 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 nonimmune mediated mechanism, but does not specific severity.

Endpoint Determinant Score – Skin Corrosion and Irritation

The availability of adequate data to support conclusions provided in authoritative reviews can be based on (1) observational information in humans who are topically exposed to a chemical 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 nonimmune mediated mechanism in experimental animals. If data that can be used for banding have been provided by the authoritative reviews, this contributes an EDS of 5 in the overall assessment of whether sufficient information is available for banding a chemical in Tier 2. This EDS is assigned on the availability of the information, irrespective of the outcome of the test or observation (positive/negative).

3.11. Banding Potentially Hazardous Chemicals 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 2013].

Data Sources – Eye Damage/Irritation

Sources for Tier 2 information for Eye Damage/Irritation can be found in Table 3-24.

Table 3-24: Data Sources for Eye Damage/Eye 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 & 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 based on its capacity to cause serious eye damage or irritation are gathered and evaluated from authoritative reviews conducted by governmental, national, international, and professional agencies with interests in the human health impacts of hazardous chemicals (Table 3-24). 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/eye irritation endpoint. Instead, NIOSH recommends assigning bands on the basis of qualitative data provided by authoritative reviews as shown in Table 3-25.

Table 3-25: Criteria for Eye Damage/Eye Irritation Endpoint

NIOSH Banding Criteria for **Serious Eye Damage/Eye Irritation**			
Endpoint Band			
A	**B**	**C**	**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

Data Quality Assessment Parameters – Eye Damage/Irritation

The following provides information on the potential of a substance to be assigned a band based on the Eye Damage/Eye Irritation endpoint:

- Conclusions provided in authoritative reviews (e.g., ATSDR, IRIS, OECD SIDS, ECHA dossiers)
- When multiple classifications by various authoritative reviews exist, the most health protective band corresponding to the classifications is selected (Table 3-25)

Endpoint Specific Band Selection –Eye Damage/Eye Irritation

(1) Assign band E if the substance is characterized as causing *irreversible eye* damage.
(2) Assign band C if the substance is characterized as a *severe eye irritant, moderate to severe eye irritant*, or if results are mixed.
(3) Assign band B if the substance is characterized as *mild to moderate irritation*.
(4) Assign band A if the substance is not an eye irritant.

Endpoint Determinant Score – Eye Damage/Eye Irritation

The availability of adequate data to support conclusions provided in authoritative reviews can be based on (1) observational information in humans who are splashed in the eye with a chemical or exposed to its vapor in the workplace or in an emergency situation and/or (2) experimental data on eye corrosion and irritation in experimental animals. If a conclusion has been provided by the authoritative reviews, this contributes a determinant score of 5 in the overall assessment of whether sufficient information is available for banding a chemical in Tier 2. This score is assigned on the availability of the information, irrespective of the outcome of the test or observation (positive/negative).

3.12. Issues of Certainty Bounding Band Selection

In deriving a TDS as an index of data sufficiency for banding, the measure 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 associated with multiple studies of each endpoint, it is likely that varying degrees of certainty on band selection will be determined for chemicals where the TDS is similar. This is to be expected, and users may wish to take this factor into consideration when banding chemicals. NIOSH has not developed specific guidance on this point.

3.13. Applicability and Suggested Rules for Using Human Data for Hazard Banding

This section addresses the use of qualitative and quantitative human data in band selection at the Tier 2 level. For endpoints where a dose-response analysis and the identification of a toxicity threshold is required for band selection (reproductive and/or developmental toxicity, specific target organ toxicity through repeated exposure, and carcinogenicity), the desirability of using quantitative human data centers on the possibility of reducing uncertainty in extrapolating dosimetric data obtained in experimental animals to health deficits that might occur in exposed humans. However, toxicological data in environmentally or occupationally exposed human cohorts are often beset by imprecision in the exposure term, uncertain duration, and the likelihood of concurrent exposure to other chemicals. In practice, therefore, comparatively few well-documented human exposure data sets are available for dose-response analysis and band selection.

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. Simple statements covering the presence of an effect or the severity of the outcome (no effect, mild, severe) may contribute to our understanding of the possible impact of the chemical on these endpoints, and thus apply to their banding, in accordance with applicable technical criteria. 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 the following criteria apply:

(1) The data have been obtained from Rank 1 sources.
(2) Agencies have used them to develop toxicity benchmarks, such as an RfC (U.S. EPA) or MRL (ATSDR).
(3) A dose-related response is evident from the principal study, with a clearly defined NOAEL.

NOTE: *The use of human exposure data from Rank 2 sources is not recommended for banding because, in many if not all cases, the dosimetry is likely to be less reliable, and, by analogy to the rules for determining an animal-specific NOAEL, the dose-dependent human health deficits and related points-of-departure may be less clear-cut.*

Example where human exposure data are applicable

- The U.S. 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 study with a decline in lung function as the primary effect [Diem et al. 1982]. A LOAEL of 0.014 mg/m^3 (0.0019 ppm) was given in the summary. **Band E** would apply to these findings.

An example where animal data better define the primary effect, though supported by human exposure 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. However, because these reports contain imprecise information on exposure levels, the U.S. 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) placing the chemical in **band D**. Surveying the accounts of epidemiological studies and reports in the IRIS toxicological review of n-hexane suggests a point-of-departure for the critical effect in the vicinity of 50 ppm, also applicable to **band D**. However, the latter estimate, while useful as a check, would itself be inadequate as the primary source for banding because it was not used to develop the RfC, and precise dose-response information is generally lacking.

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 simple summary statements to be found in secondary sources such as HSDB, EHC documents, and from other secondary documents as may apply to the chemical under evaluation.

Example

- An illustration of the process may be obtained from consideration of the HSDB record for styrene. A suggested procedure would be to open the record for the chemical and (1) click on *Human Health Effects*; (2) track down through the record to the subheading *Skin, Eye, and Respiratory Irritations*; (3) document any relevant findings from the short paragraphs given in this section. For styrene, the chemical is said to be *irritating to skin*, and that *exposure to concentration of styrene above 200 ppm causes irritation of the eyes and respiratory tract*. **Band B** would be a reasonable selection for both outcomes, on the basis of these statements. However, a more precautionary band selection might be

warranted if skin and eye tests in animals give a more severe outcome such as skin corrosion or other irreversible effects.

3.14. OEB – Considerations for Application of the Range of Concentrations

The occupational exposure banding process uses a set of endpoint-specific criteria to identify the hazard-based band most representative of the health effects profile for the chemical being evaluated. Each band corresponds to a range of airborne concentrations to assist with risk management decisions.

The OEB range that is the product of the banding procedure contrasts with a traditional OEL, which is typically represented as a single value for risk management purposes. Despite the difference in the OEB and OEL derivation process, the interpretation and use of the band and associated concentration range is not very different from traditional occupational hygiene practice for OELs. The practical similarity in OEBs and OELs stems from the fact that OELs are not precise estimates of a cut-point between safe and dangerous. 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 (which often are order of magnitude estimates). Like most OELs, an OEB can be used as a TWA with a specific duration of time, such as 8 hrs. An OEB can also be used for shorter durations, such as a 15-min STEL when useful. The range of uncertainty in an OEL depends on the level of confidence in the underlying data and the extrapolation involved. Overall, the OEB identified in using the procedure in this NIOSH guidance is intended to provide a credible range for risk management. Consequently, the NIOSH process requires a risk management structure that can accommodate the use of a range of guide values.

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 a key component of existing control banding techniques. The value of such a 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. Based on such an approach, an organization implementing the occupational exposure banding process might have a default suite of control requirements for each band. Thus, band A chemicals might require only standard workplace precautions, while a band E chemical 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 this case the lower end of the band is often used as the default 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.

As an alternative to the use of a categorical approach, the OEB allows for further customization of risk management procedures by selecting a guide value range within the OEB. Some stakeholders may select a guide value range of 10% of the OEB range, whereas others use a guide value range including the median, or 75% of the OEB range. The decision of a guide value range should be based upon 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 does, as written.

3.15. 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). As for any chemical, 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 or other systemic targets following uptake into the blood). For airborne microscale and nanoscale (between 1 and 100 nanometers) particles, the amount (e.g., total mass or surface area of the aerosol) that reaches and deposits in the target site 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 across all particulate 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 2011]. 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 2011]. Other physical and/or chemical properties can also influence the degree of toxicity observed for inhaled particles (e.g., size, shape, surface reactivity, solubility). Examples of particle categories include liquid aerosols, fibers, and nanoparticles (defined as particles having at least one dimension of the primary particles <100 nanometers [BSI 2007; ISO 2007, 2008; NIOSH 2009a; ISO 2014]). Recommendations for the application of the occupational exposure banding process for particles in these categories are described in this section.

Liquid aerosols. Particulates in the liquid phase can be evaluated using the general occupational exposure banding process regardless of aerodynamic diameter. This reflects that 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. Fibers have unique aerodynamic features that are dependent on their geometry (e.g., length-to-width aspect ratio and cross-sectional diameter) and influence their deposition in the respiratory tract. In addition, the physical shape and size of fibers can directly influence toxicological properties and the nature of their interactions with target cells. These complexities require approaching fibers with a Tier 3 assessment, and the OEB criteria are not recommended [Hinds 1982].

Nanoscale solid-phase particles. For the purpose of this document nanoscale particles are defined as those particles with primary particle diameters less than 100 nanometers [NIOSH 2009a]. Significant evidence indicates that for some poorly soluble particles, increases in toxic potency occur for a chemical when comparing the same mass dose of microscale and nanoscale materials (see review in NIOSH [2011]). However, the total particle surface area dose retained in the lungs in rodents was a good predictor of adverse lung effects [NIOSH 2011]. This finding has led to the conclusion that dose in terms of "total mass deposited" does not always adequately predict dose-response behavior or toxic potency across particle sizes. This difference might 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 [ANSES 2010; ISO 2014]). On the basis of similar criteria, NIOSH recommends that the occupational exposure banding process — when applied to nanoparticles — are modified according to the following guidelines:

- ***Poorly-soluble nanoscale particles:***

If the toxicity data include NOAELs that were developed specifically for the nanoscale form of the chemical, the NIOSH occupational exposure banding process can be used directly with no modifications.

If data are only available for the microscale form of the chemical the band assignment should be shifted to the next most potent band on the assumption that poorly soluble nanoscale agents will likely be an order of magnitude more toxic that their microscale equivalents.

This assumption is supported by evidence of an approximately 10-fold higher potency for some nano-diameter poorly-soluble particles compared to the same mass dose of micro-diameter particles (reflecting an approximately 10-fold difference in specific surface area, e.g., 5 vs. 50 m^2/g) [NIOSH 2011].

- ***Soluble nanoscale particles:***

  Data support a role of increased total particle surface in the increased toxicity associated with poorly-soluble nanoscale particles as discussed above. Thus, because the retained surface area is lower over time for soluble particles (due to dissolution), increased solubility would decrease the potency of particles *if* the adverse effects are due to the retained particle surface dose. On the other hand, higher solubility could result in increased potency (compared to poorly soluble particles) if the toxic effects are due to released ions. Ions can react with cells at either the site of entry, such as lungs, or in other organs, potentially causing tissue damage and decreased organ function at certain doses. Particle size may play less of a role in the toxicity of higher-solubility particles assuming similar molecular concentrations and ion release rates. 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 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, acceptance of these general conclusions requires caution because of limited data on which to evaluate their effectiveness. For example, data and methods are not yet available to predict adverse effects solely on the basis of specific physical-chemical properties, such as solubility. Moreover, moderately soluble particles may elicit effects related to both their particulate and solute components. Despite these knowledge gaps on the role of nanoscale characteristics on the potential toxicity of inhaled particles and fibers, some aspects of the enhanced toxicity observed with inhaled nanoscale particles may relate to higher respiratory tract deposition and bioavailability (which would also occur regardless of particle solubility). Given these uncertainties, it is recommended 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 most potent band if data are only available for the microscale form of the agent.

- ***Nanoscale fibers (or tubes):*** Since the toxicity of nanoscale fibers and nanoscale tubes may differ significantly 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 chemicals. Therefore, tier 1 and tier 2 should not be used. Instead, a Tier 3 assessment is required as described for other fibers.

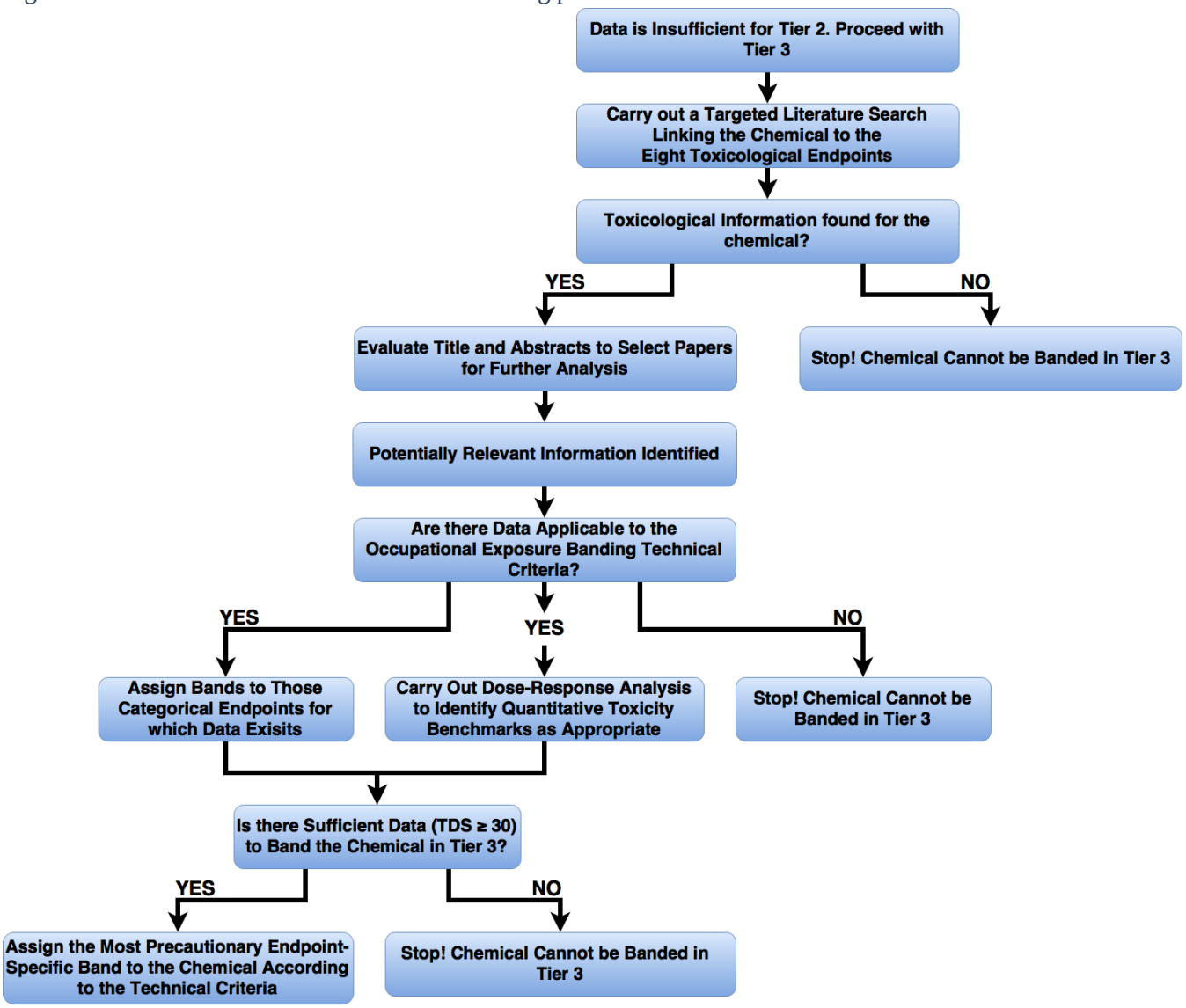
These general recommendations are considered precautionary in nature. Limitations in the available scientific information include uncertainty in the mechanisms of potential potency differences in toxicity of nanoscale vs. microscale particles of various chemical composition, surface properties, shape, degree of agglomeration, etc. The number of chemicals with adequate data for such size-based toxicity comparisons is small, which prevents drawing firm conclusions at this time about relative potencies among various particle types and sizes. NIOSH is currently evaluating the state of the science for deriving OELs or 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 chemicals to human health-related exposure bands. In Tier 1, this is based on information abstracted from GHS. In Tier 2, it is based on data summarized in authoritative secondary sources. However, the process recognizes that some chemicals may not be amenable to these processes because of insufficient information. If a user desires to scrutinize the potential human health impacts of a chemical 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 effects 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.

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 under consideration, (2) selecting studies of the chemical 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 toxicological outcomes, including any available dose-response information. The latter 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 chemicals 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 4-1.

Figure 4-1: Flow chart for the Tier 3 hazard banding process



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 or its CAS No. to the appropriate toxicological and human health outcomes should be constructed. The search should cover the period from the year before the most recently published authoritative review to the present, or for an unlimited period if there are no agency-sponsored documents covering the subject chemical.

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 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. While the primary toxicity benchmark for banding is the NOAEL, persons examining the data may need to derive other appropriate benchmarks such as the LOAEL, BMDL, BMCL, or, for cancer incidence data, the SF or IUR. It is assumed that individuals carrying out the Tier 3 evaluation will be familiar with these procedures. Factors to consider include power, standard procedures, model, and limitations. In addition, evaluating the reliability of the toxicological data by use of procedures such as the Klimisch score should be considered.

In conducting an assessment, a method to differentiate study quality or reliability should be employed. 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 to be "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., unphysiologic 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 to be "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 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 health-protective band within and among endpoints should be selected as the overall band.

Judging Data Sufficiency

Information availability on the toxicological endpoints of interest provides critical input on data sufficiency in a similar manner to that described for Tier 2. The existence of data on a particular endpoint (for example, reproductive/developmental toxicity) contributes to a determinant score 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 cannot be banded beyond the default within the NIOSH process.

Assessing Uncertainty

In a similar manner to the Tier 2 evaluation, it is recognized that 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 chemicals where the TDS is above the threshold for sufficiency. Users should also 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 OEL Ranges

After arraying the hazard data for each endpoint, the appropriate overall OEB for the chemical is determined considering all endpoints together. Each of the bands is associated with a range of exposure 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 for their application in risk management decision making. The ranges reflect likely values for a health-based OEL given similar health hazard. However, the OEL ranges are designed only as a potential exposure control ranges. While it is most 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 insufficient or more than adequate.

Selecting the OEL Range Category

Two possible OEL ranges are associated with each band, reflecting the need for exposure control ranges that differ for chemicals in different physical forms. Guidelines for selecting the OEL range category are as follows:

- The OEL range for bands for exposures to chemicals that are present in the form of gases or liquids that can form vapors in the occupational environment is provided in units of parts per million (ppm).
- The OEL range for bands for exposures to chemical that are present in the form of solid particles is provided in units of mg/m^3.
- Some chemicals that are liquids at standard temperature and pressure have sufficiently low vapor pressures that occupational exposure can occur in both the particulate phase (as liquid aerosols) and vapor phase. Such chemicals should generally be compared to the OEL range category for gas/vapor phase exposures (see details below).
- The OEL ranges for each band are specific to each physical form and were evaluated against health-based OELs for chemicals of similar physical characteristics; thus, gas or vapor phase chemicals **should not be converted** to units of mg/m^3 for OEL range selection. Rather the OEB is determined first, and the related OEL range corresponding to that band is provided in the NIOSH occupational exposure banding process.

OEL Range Concentrations Differ by Physical Form

The values of the OEB concentration ranges were developed on the basis of experience in field application of hazard banding processes and evaluation against existing OEL databases. The need for different OEL concentration ranges by physical form is based on the observation that the distribution of OELs for gases and vapors is shifted to higher concentrations when compared to particles when both forms are represented in units of mg/m^3. For example, a relatively low potency chemical vapor such as acetone has a NIOSH REL of 250 ppm (590 mg/m^3). In the context of controlling exposure to particulate exposures, a concentration of 590 mg/m^3 is well above the allowable limit for even inert solid particles, which often have OELs in the range of 1 to 10 mg/m^3. Note that the distributions do overlap, and thus clearly some vapors are more potent than some particles on an mg/m^3 basis.

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

- An upper bound limit on exposures to solid particulates relates to physical mechanisms in the lung for overloading of normal particle clearance. This particle overload phenomenon caps the potency distribution for particles, but is not relevant for gases and vapors.
- Many toxic chemicals exert their effects at the level of the tissue response on the basis of local tissue dose. Thus, for a given total mass of chemical inhaled, the larger the surface area contacted, the lower the tissue concentration of the chemical at any single tissue location. Thus, for soluble particles, the local tissue dose can be higher for a given total exposure due to high deposition site doses compared to gases and vapors that are governed by dose diffusion.
- For insoluble particles overall respiratory tract retention time is often higher than for gases and vapors. To the degree that such particles induce a toxic response, the cumulative dose (reflecting local dose and amount of time the tissue is exposed) can be higher for solid particles compared to gases and vapors.
- The relative biological activity of low vapor pressure liquids is complex because such chemicals have properties that are intermediate between gases and solid particles. On the basis of analysis of health-based OELs for such low vapor pressure liquids, the OEB ranges identified on the basis of the NIOSH 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 particles in terms of clearance and local tissue doses. However, the less soluble and lower the vapor pressure the more like a solid particle such liquids will act. For liquids at the extreme end of the range for such properties both OEL range categories can be evaluated with recommendations to apply the band that is the most protective one recommended because liquids at either extreme may have properties that more closely resemble that of either gases or solids. Such evaluations could occur as part of an expert evaluation through a Tier 3 assessment.

To avoid the confusion in these differences by physical form, the occupational exposure banding process uses ppm as the preferred concentration units for gases/vapors. For solid particles, the bands are based on mg/m^3.

5.2 Mixed Exposures

Introduction

Workers from agriculture, construction, mining and other industries are commonly exposed to combinations of chemicals, biological or physical agents, and other stressors. However, knowledge is limited about potential health effects from mixed exposures. Research has shown that physiological interactions from mixed exposures can lead to an increase in severity of the harmful effect. For example, exposure to noise and the solvent toluene results in a higher risk of hearing loss than exposure to either stressor alone. 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 mixed exposures is a complex issue, given the large number of combinations that occur every day in a variety of workplaces and in our everyday life experiences.

History

Over the years NIOSH has published RELs for various mixed exposures within criteria documents and current intelligence bulletins. The process applied for mixed exposures has been unique depending upon the mixed 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 (NORA), the NORA Mixed Exposures Team was established to facilitate the study of occupational mixed exposures. In December, 2004, the NORA 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 [NRC 2009]

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 but not limited to the following processes:

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 mixture in the same way that one is conducted for a single chemical. 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 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 only be used when synergy is not expected or known.

Special consideration should be given when banding chemicals comprised of a mixture of two or more chemicals. If health effect literature for the mixture exists, it should be used to band the chemical. If health information does not exist for the mixture, practitioners will band each chemical constituent independently in order to conduct OEBs for mixtures exposures. The resulting bands from chemical constituents will then be compared, and the most protective band will be selected for the mixture.

Employees may also be exposed to several individual chemicals at the same time in the workplace. In these situations, the OEBs should be conducted independently by chemical. These bands will be considered chemical by chemical in this mixed exposure. Care should be taken to determine if there are any synergistic effects of the mixed exposure.

Chapter 6 : Preliminary Evaluation of Tier 1 and Tier 2 Protocols

Accuracy and usability of the NIOSH Occupational Exposure Banding Criteria are important to the success of the process. In order to evaluate the occupational exposure banding decision logic, NIOSH answered the following questions:

- Do the banding criteria reflect toxicity as determined by an independent evaluation (e.g., OELs)?
- Are the banding criteria consistent and specific when applied by independent users?
- Are some health effect endpoints more reliably banded than other health effects?

These evaluations provide additional confidence that the tool can be used effectively and consistently by stakeholders.

6.1. Evaluation of Tier 1 Criteria

Although NIOSH does not recommend banding chemicals with existing OELs, they are potential indicators of health hazard and potency. To evaluate the Tier 1 process, NIOSH compared the OELs of 804 chemicals to the Tier 1 OEBs for the same chemicals. OELs are not a perfect standard for comparison; however, they represent the current level to which chemical hazards are controlled. The chemicals selected for this exercise are all chemicals that have been assigned at least one full shift OELs, including NIOSH RELs, OSHA PELs, Cal/OSHA PELs, German MAKs, ACGIH TLVs, and AIHA WEELs.

During the evaluation, NIOSH determined whether the assigned OEB range included the existing OEL value for that chemical. The criterion for acceptance of the Tier 1 evaluation was that the assigned OEB would either contain the OEL or be more protective than the OEL for more than 80% of the chemicals. Based on other commonly used validation criteria, eighty percent was used rather than a lower percentage because the team determined it was the minimal level which provided confidence in the comparison. A higher percentage was not selected as it might diminish the usefulness of the OEB methodology. If the Tier 1 banding protocol was at least as protective as the OEL at least 80% of the time, this would demonstrate successful assignment of the GHS codes to OEBs. When more than one OEL was available for a substance, the lowest OEL was used for comparison. This step would further diminish bias that might be inherent to OELs based on the age for the OEL and the agency that it originated from. Table 6-1 below shows which type of OEL was utilized to conduct the comparisons. Note that the sum of sources in Table 6-1 is greater than 804 because nearly half the time the minimum OEL was the same value from 2 or more sources. The minimum OEL came from 2 sources 118 times, 3 sources 134 times, 4 sources 92 times and 5 sources 37 times.

Table 6-1: Sources of OELs for the Tier 1 Evaluation exercise

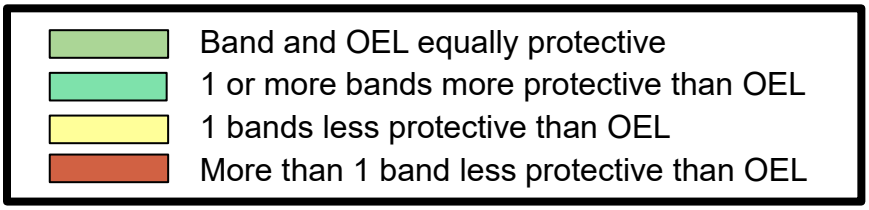
Source of minimum OEL	Frequency
TLV	448
MAK	204
WEEL	106
NIOSH REL	324
CAL PEL	356
OSHA PEL	176

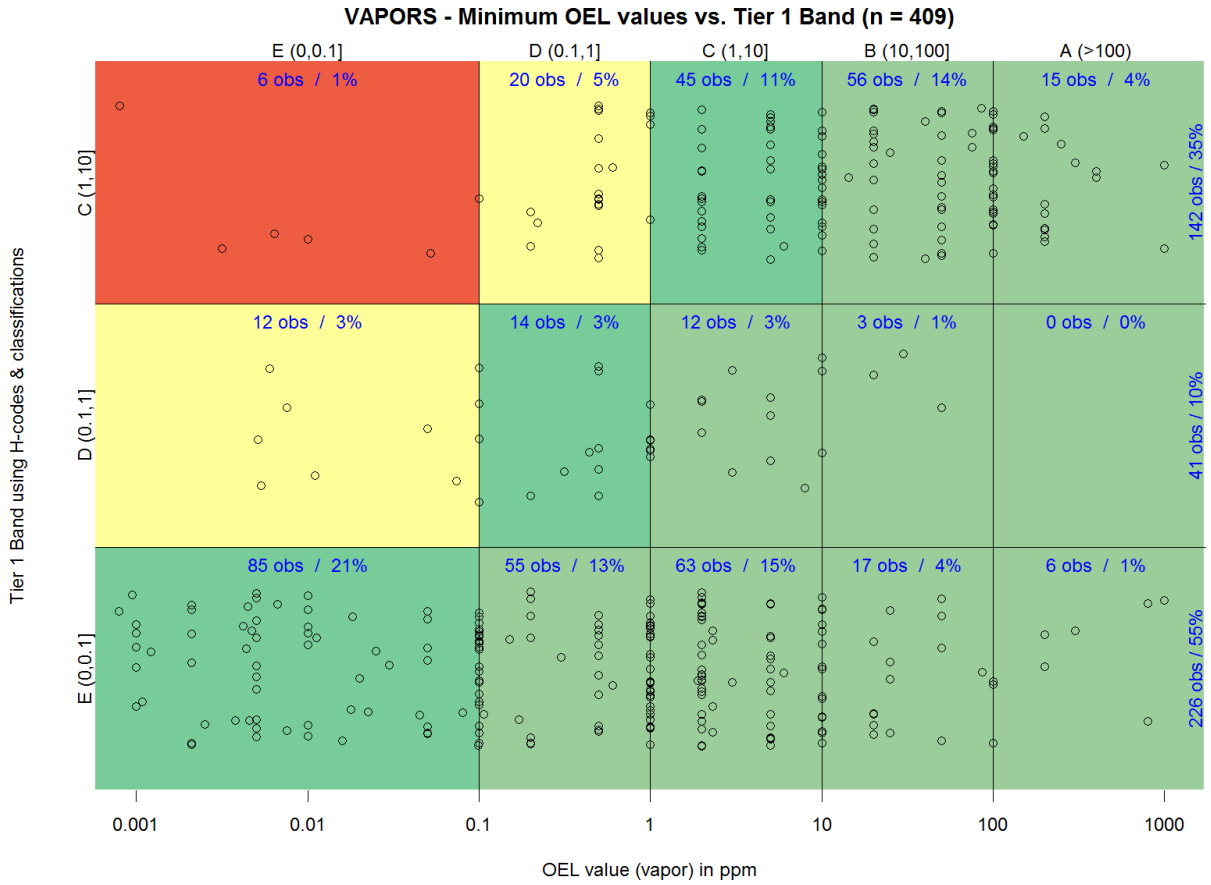
** Sum is greater than 804 because the minimum OEL came from 2 or more sources 381 times.*

NIOSH was able to retrieve GHS hazard codes and categories from the GESTIS database for 600 of the 804 chemicals. This data was used as the basis of our Tier 1 comparison. There were 409 gases/vapors and 191 dusts/particulates evaluated against the Tier 1 criteria based on GHS hazard codes and categories.

In the figures below, the OEL on the x-axis is compared to the Tier 1 band on the y-axis. Each circle on the figures represents an individual chemical. The color of the areas within the figure represent the level of protection that the OEB offers compared to the OEL. For vapors (Figure 6-1), 91% of the chemicals were assigned a band in Tier 1 band that is at least as protective as the OEL used for comparison. These chemicals fall within the green portion of the figure. For 32 of the 409 chemicals (8%), the Tier 1 band was one band less protective (shown in yellow) and for 6/409 chemicals (1%), the Tier 1 band was two bands less protective (shown in red).

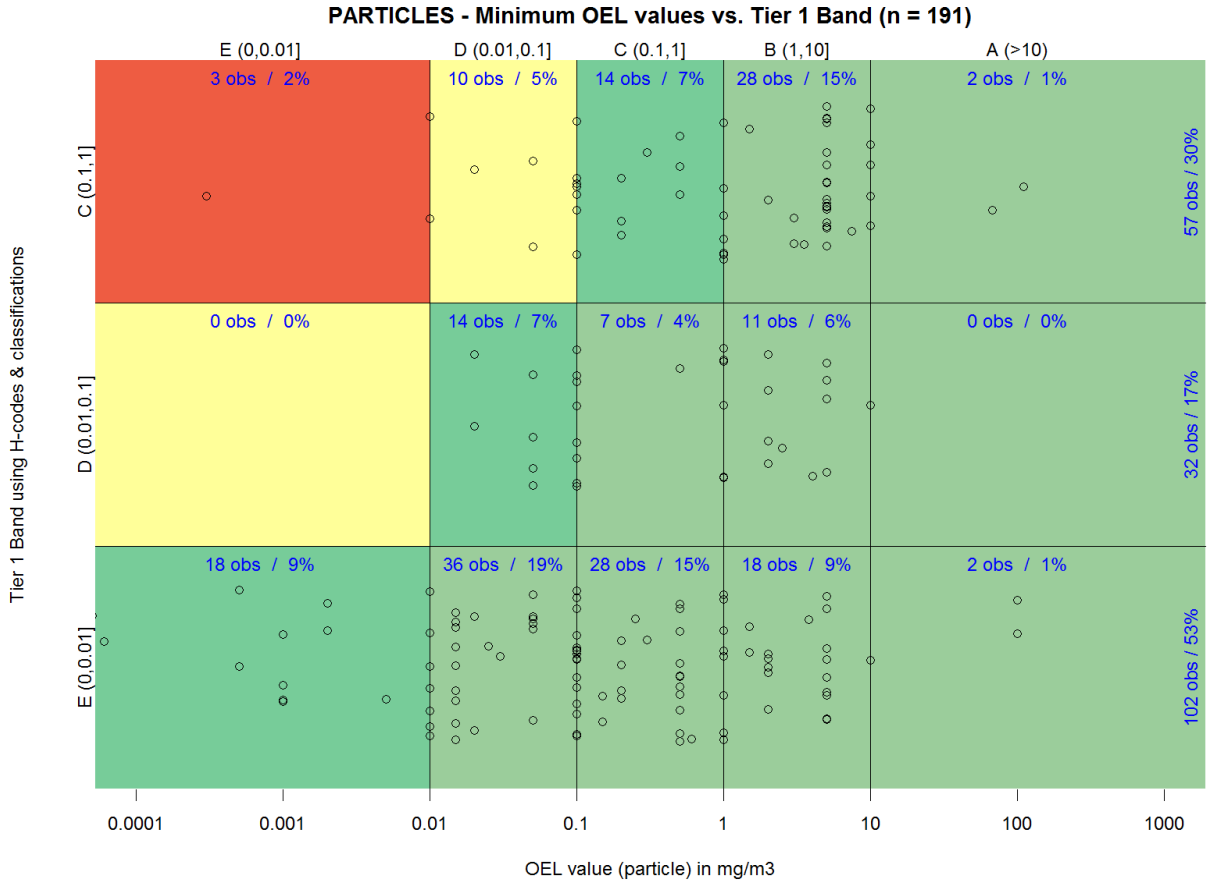
Figure 6-1: OEL values vs. Tier 1 band for vapors





For particles (Figure 6-2), 93% of the chemicals banded in Tier 1 were assigned a band that is at least as protective as the OEL used for comparison (shown in green). For 10/191 chemicals (5%), the band was one band less protective (shown in yellow) and for 3/191 substances (2%) of the time, the band was two bands less protective than the OEL (shown in red).

Figure 6-2: OEL values vs. Tier 1 Band for Particles



The overall agreement between the Tier 1 process and the derived OEBs exceeded the NIOSH a priori hypothesis. This exercise provided confidence that chemicals banded with the Tier 1 process would be appropriately classified according to their potential to cause adverse health effects. However, the process did not band chemicals with 100% accuracy. This may be due to variability in how the OELs were set, policy decisions inherent within the creation of the OEL, or new information reflected in either the OEL or limited information available to GHS hazard code. Given this result, NIOSH recommends users to take advantage of the increased information available in Tier 2 in order to increase the reliability of the banding and recommends that the Tier 2 process be completed for all chemicals when user expertise and adequate data are available.

6.2. Evaluation of Tier 2 Criteria

Tier 2 banding requires the user to access authoritative summary online information sources specified in the NIOSH criteria to assign a band for each health endpoint. There are quantitative criteria for some endpoints, such as LD_{50} values for acute toxicity and the EPA IRIS inhalation unit risk value for cancer potency. Other endpoints, for example, genotoxicity, have qualitative criteria, such as "negative results," "mixed results," and "positive results."

Sources of information are specific authoritative summaries of toxicity information. As an example, for carcinogenicity, the sources are: U.S. National Toxicology Program Report on Carcinogens, U.S. EPA IRIS, International Agency for Research on Cancer, Health Canada, and State of California Office of Environmental Health Hazard Assessment. The list of recommended sources for all 9 health endpoints are provided in Table 3-2.

Instructions are provided on how to evaluate the information in each source to determine an occupational exposure band. For example, if the inhalation unit risk calculated by U.S. EPA was 0.002 per $\mu g/m^3$, that would correspond with band D for cancer potency. See section 3.2 of the guidance document for complete details on the Tier 2 cancer evaluation. Sections 3.2-3.9 contain details on Tier 2 evaluation for all nine health endpoints.

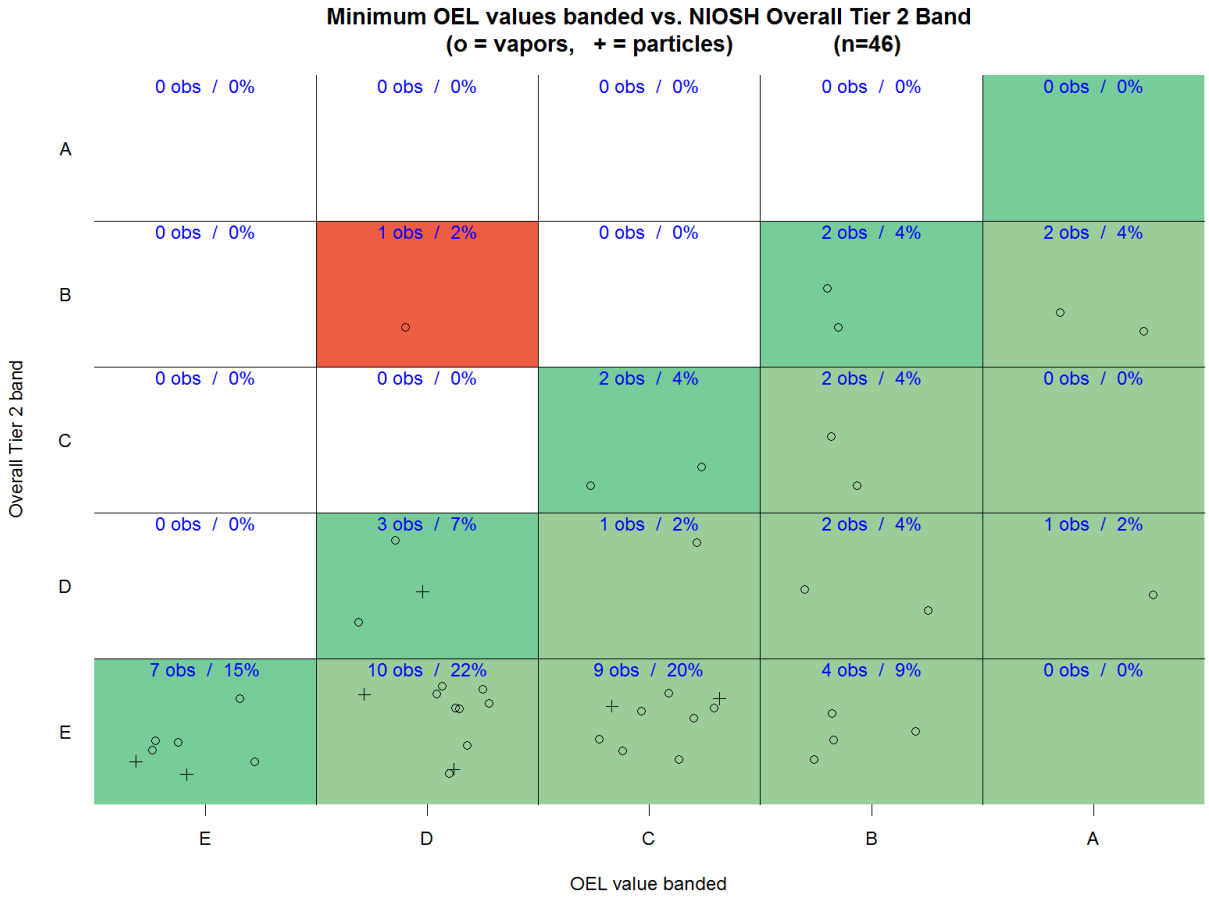
Once all the sources for each health endpoint have been reviewed and the corresponding bands for each endpoint ascertained, the overall OEB is calculated, based on the bands derived from each endpoint and the TDS. The TDS is the sum of the endpoint determinant scores (EDS) that reflect the presence or absence of data on each endpoint, weighted to consider the most serious health endpoints more heavily. The final overall band is selected as the most health-protective endpoint band once a TDS of 30 is met. The exception to this is if one of the endpoint bands is band E in which case there is no threshold for the TDS. The details on data sufficiency and TDS can be found in section 3.0.

Comparison of Tier 2 Bands with OELs

To evaluate the Tier 2 process, NIOSH compared the OELs of 53 chemicals to the Tier 2 OEBs for the same chemicals. This analysis was done similarly to the tier 1 evaluation. Although OELs are not a perfect standard for comparison, they represent the current level to which chemical hazards are controlled. To answer the question, "Do the banding criteria reflect toxicity as determined by an independent evaluation (e.g., OELs)?" Fifty three chemicals were banded by NIOSH users in the Tier 2 process and compared with existing OELs. NIOSH selected the chemicals from the EPA IRIS database, the TLV "Under Study" List, the MAK list of "Substances for which no MAK value can be established at present", and chemicals listed on Health Canada. As in the Tier 1 comparison with OELs, the NIOSH target was to have the Tier 2 band at least as protective as the OEL at least 80% of the time.

In Figure 6-3, the band with the exposure range containing the OEL is displayed on the x-axis and is compared to the Tier 2 band on the y-axis. Of the 53 chemicals attempted, Tier 2 banding was completed for 46 chemicals. Of those 46 chemicals, the Tier 2 band was at least as protective as the OEL used for comparison (shown in green) for 45 chemicals (98%). For 1/46 chemicals (2%), the band was two bands less protective than the OEL (shown in red). The 7 chemicals that could not be banded in Tier 2 had OELs that fell in the range corresponding to band B (3 chemicals), band C (3 chemicals), and D (1 chemical).

Figure 6-3: Minimum OEL values banded vs. NIOSH overall Tier 2 band



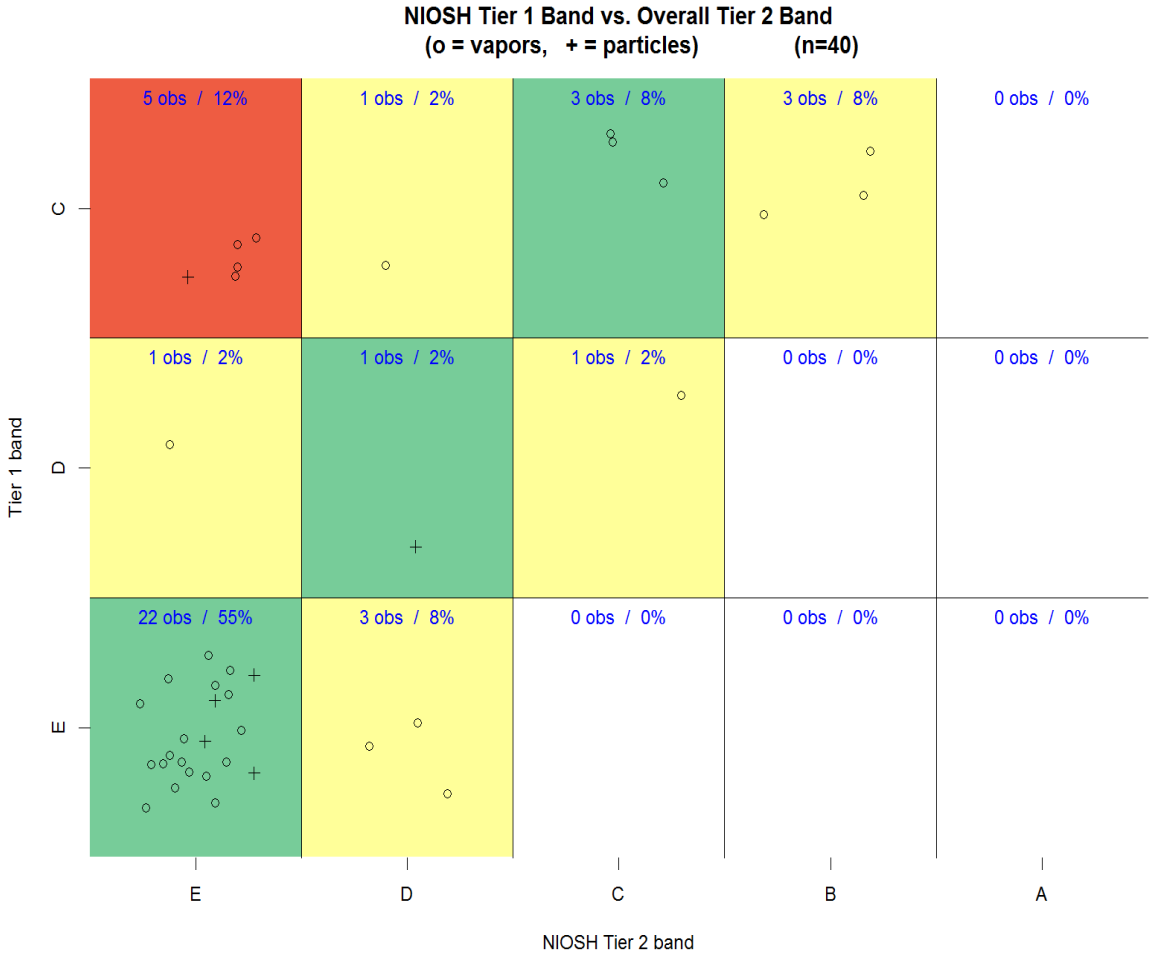
Comparison of Tier 1 and Tier 2 Banding Results

Reviewers banded a sample of 53 of the original 804 chemicals in both Tier 1 and Tier 2. The target was that more than 80% of the time the Tier 1 band would be at least as protective as the Tier 2 band. Forty of those 53 chemicals had sufficient information to be banded in both Tier 1 and Tier 2. One chemical could not be banded by either Tier 1 or Tier 2, six chemicals were banded in Tier 1 but sufficient information was not found to band them in Tier 2, and six

chemicals that did not meet the criteria for banding in Tier 1 had sufficient information to band them in Tier 2. The results are shown in Figure 6-4. Twenty-six chemicals were assigned identical bands in Tier 1 and Tier 2. Nine chemicals had Tier 1 and Tier 2 bands that were one band different and five chemicals were banded 2 bands different.

For 65% of chemicals, there was perfect agreement between Tier 1 and Tier 2 bands. For 17.5 percent of chemicals, Tier 1 is more protective than Tier 2. For another 17.5 percent, Tier 2 is more protective than Tier 1. Tier 1 is at least as protective as Tier 2 for 82.5% percent of the chemicals, which the initial target. These results further support our recommendation to always conduct a Tier 2 assessment.

Figure 6-4: Comparison of Tier 1 vs. Tier 2 bands



Evaluation of Tier 2 Criteria- Consistency

Tier 2 criteria were evaluated for accuracy and usability by comparing the results across potential users. A total of 43 reviewers were recruited to evaluate the process. They were all occupational hygienists or had knowledge of occupational hygiene principles.

Each reviewer received 4 hours training developed by the NIOSH team. The amount of time required to teach and demonstrate the Tier 1 process to users was relatively short. Significantly more time was necessary to train users effectively on Tier 2. Each reviewer received two chemicals (Chemical 1 and Chemical 2), blank data sheets, and a copy of the banding criteria document. Reviewers emailed their results, and they were compiled anonymously. Of the recruited reviewers, 18 completed the full process and submitted banding information.

Tier 1 results (requested from half the reviewers) were identical for all reviewers for both chemicals. Tier 2 results (requested from all reviewers) showed that the overall band had much less variability than the individual endpoints. For Chemical 1, 12/16 found band D. One reviewer banded this chemical in band C, one in band E, and 2 in band B. One reviewer did not band this chemical and another did not complete the banding process. For Chemical 2, 12/18 banded this chemical in band E, and six banded it in band D.

Acute toxicity was the most consistent individual endpoint among reviewers who banded this endpoint, 13/17 and 14/18, assigning identical bands as shown in Figure 6-5 and Figure 6-6. The band assigned for other health endpoints showed had more variability. Reproductive toxicity responses ranged from band A to band E for Chemical 1 and from band A to band C for Chemical 2.

The total determinant score (measure of presence of data for each endpoint) varied across reviewers. For Chemical 1, the scores ranged from an insufficient 25 to 105, mean = 84 +/− 21. For Chemical 2, scores ranged from 40 to 110, mean = 83 +/-25.Results are presented in detail in Table 6-2 and Table 6-3.

Table 6-2: Tier 2 Occupational Exposure Banding Results for Chemical 1 – 17 reviewers

Chemical 1									
	Cancer	Repro	STOT	Genotox	Resp Sen	Skin Sen	Acute	Skin Irr	Eye Irr
A	1	5		9	2	9	13	1	2
B		2	14					4	4
C	1	4	2	5				1	
D	12	1							
E		1							
No Band	3	4	1	3	15	8	4	11	11
# of Users	17	17	17	17	17	17	17	17	17

Figure 6-5: Percent Agreement among Reviewers (n=18) by Endpoint for Chemical 1

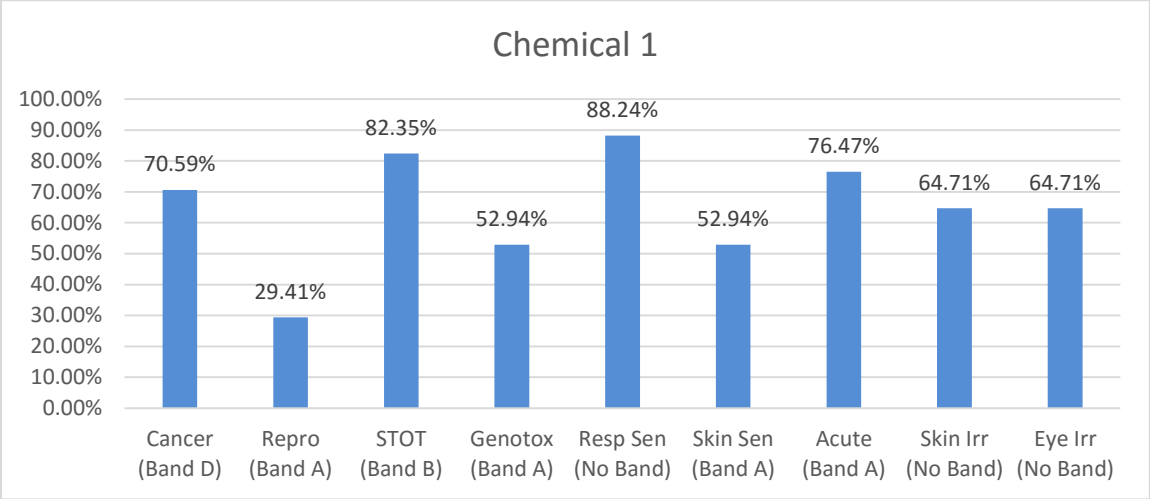
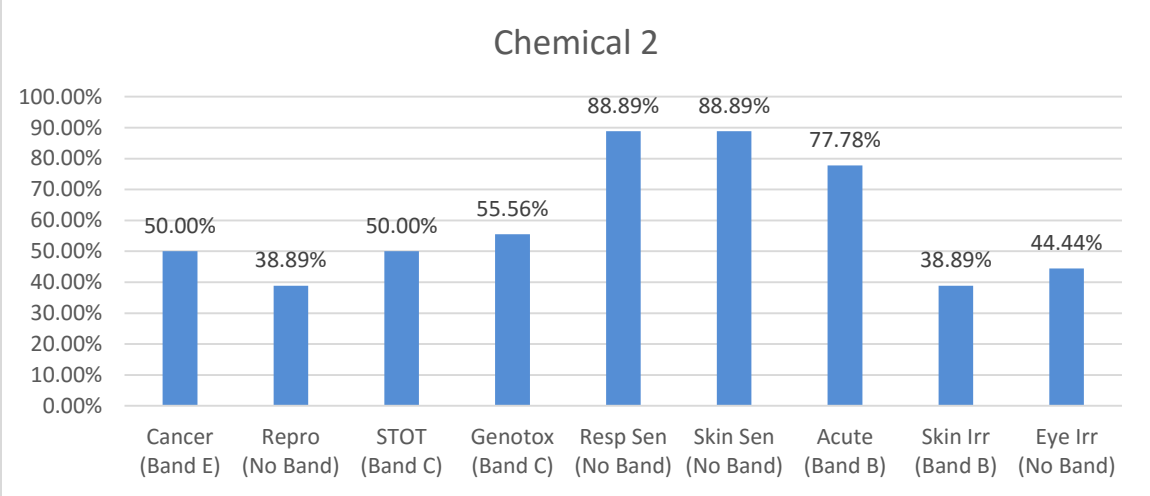


Table 6-3: Tier 2 Occupational Exposure Banding Results for Chemical 2 – 18 reviewers

Chemical 2									
	Cancer	Repro	STOT	Genotox	Resp Sen	Skin Sen	Acute	Skin Irr	Eye Irr
A		1		1	2	2			
B		6	1				14	7	4
C		4	9	10				5	6
D	8		3						
E	9		1	7					
No Band	1	7	4		16	16	4	6	8
# of Users	18	18	18	18	18	18	18	18	18

Figure 6-6: Percent Agreement among Reviewers (n= 18) by Endpoint for Chemical 2



NIOSH made comparisons between the results of the Tier 1 and Tier 2 process for these 2 chemicals. For Chemical 1, the Tier 1 band and the Tier 2 band most reviewers selected were identical: band D. However, for Chemical 2, the Tier 1 band was C while most reviewers selected band E as the overall Tier 2 band.

Closer examination of the data for Chemical 2 indicate that the overall Tier 2 band was driven by the cancer and genotoxicity information. The H-codes for cancer are H350 and H351 while the H-codes for genotoxicity are H340 and H341. None of these H-codes are present in the GESTIS Substance Database so the Tier 1 band is driven by acute toxicity, skin irritation, and eye irritation which put Chemical 2 in band C. All but one reviewer located information on cancer for this chemical which puts the Tier 2 band into E. This reinforces the NIOSH recommendation to always complete the Tier 2 banding process. Stopping with a Tier 1 band is not recommended, since the H-codes may not be complete or as up-to-date as information found in the recommended data sources.

In a separate analysis, Tier 2 criteria were examined by four reviewers to assess accuracy and usability across chemicals for 20 additional chemicals. The chemicals were chosen by toxicologists because they were expected to have data across a wide range of health endpoints. In this exercise, each chemical was evaluated by 2 reviewers applying the Tier 2 criteria. Each of the four reviewers evaluated 10 chemicals. The reviewers had various levels of expertise, ranging from expert toxicologist and experienced industrial hygienist to Masters and Doctoral level public health students. They were given a copy of a draft banding document and blank data sheets. The users emailed their results, and they were compiled anonymously.

A comparison of the results from the reviewers is presented in Table 6-4. In this evaluation, the reviewers were in agreement 100% of the time for the tier 1 band. For the tier 2 evaluation, the reviewers were in agreement 60% for the overall band, and 75% of chemicals were banded within one band. When analyzing the individual endpoints, acute toxicity had the greatest agreement (80%) whereas genotoxicity had the least (20%). For endpoints that had lower agreement, a major cause of this is that one reviewer found information for a particular endpoint when the other reviewer did not. For example, for the genotoxicity endpoint, 55% of the time one reviewer found information to band a chemical when the other did not band for that endpoint at all.

Table 6-4: Occupational Exposure Banding Results for 20 Chemicals

Endpoint	Comparison of Tier 2 Bands				
	Match	1 Band	2 Band	Band vs. No Band	Within One Band
Cancer	75%	15%	5%	5%	90%
Reproductive Toxicity	65%	15%	5%	15%	80%
STOT-RE	40%	25%	5%	30%	65%
Genotoxicity	20%	25%	0%	55%	45%
Respiratory Sensitization	50%	5%	5%	40%	55%
Skin Sensitization	40%	5%	0%	55%	45%
Acute Toxicity	85%	5%	10%	0%	90%
Skin Irritation	45%	45%	0%	10%	90%
Eye Irritation	35%	45%	10%	10%	80%
Overall Band	60%	15%	15%	10%	75%

Banding results from these 20 chemicals were used to compare Tier 2 banding with the OELs. This is shown in Figure 6.7. The Tier 2 bands in this analysis were almost always at least as protective as the OEL. When the OEL for the chemical corresponded to band E (2 of the 20 chemicals), the Tier 2 band was also E for both chemicals and both reviewers. The bands in those cases were driven by carcinogenicity (among other endpoints).

Of the 5 chemicals for which the OEL corresponded to band D, for 4 of the chemicals, at least one reviewer assigned band E, one reviewer selected band C for two of the chemicals and one reviewer did not locate information on the chemical for two chemicals. Health endpoints driving the banding included reproductive toxicity (1 chemical) and STOT-RE (2 chemicals). The remainder of chemicals were banded based on less quantitative endpoints such as genotoxicity, sensitization or irritation.

Of the 5 chemicals for which the OEL corresponded to band C, all were banded by both reviewers in band E. In two cases, one reviewer found information for the STOT-RE endpoint that drove the banding to band E. In all other cases, the banding was based on less quantitative endpoints such as genotoxicity, sensitization or irritation.

Of the 4 chemicals for which the OEL corresponded to band B, for one chemical neither reviewer found sufficient information to band the chemical in Tier 2. For the remaining 3

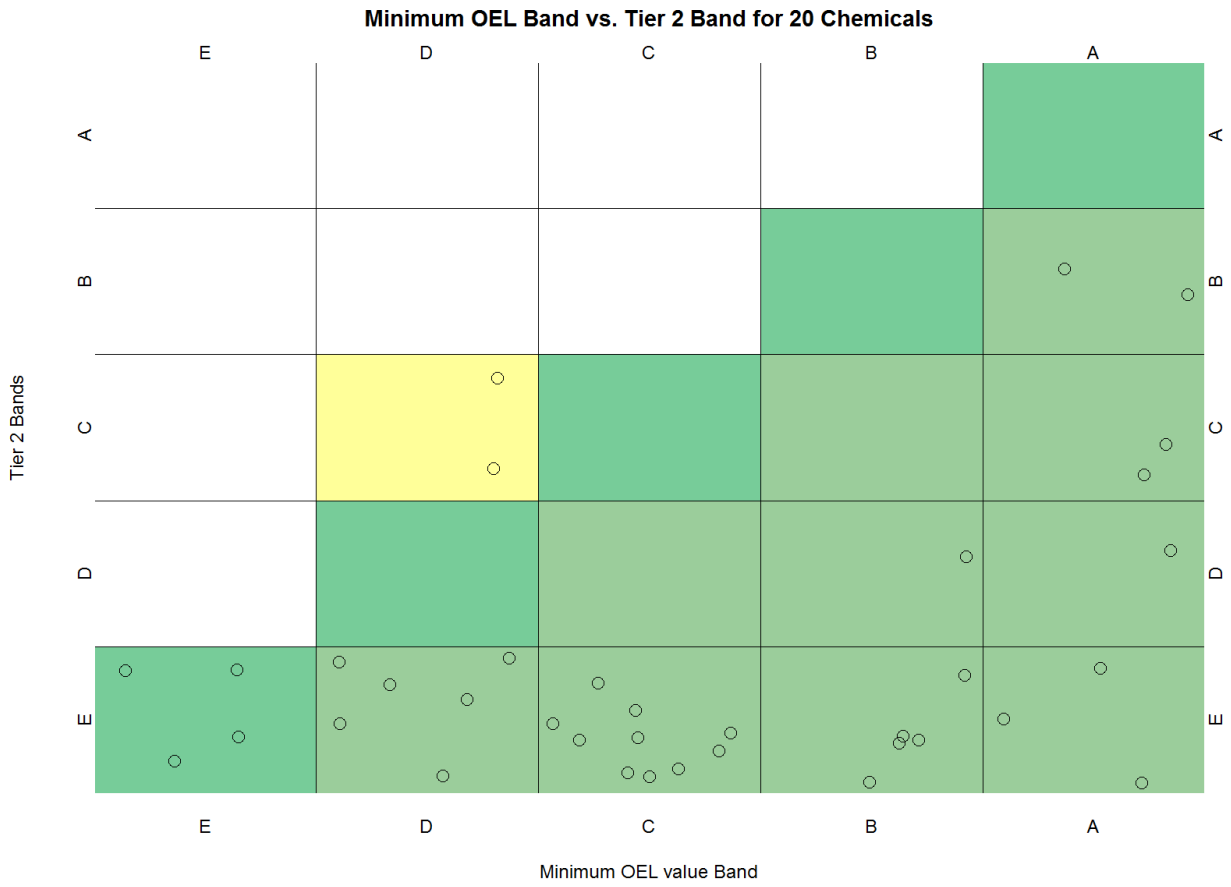
chemicals, one reviewer selected band D for one chemical, the remainder were banded as band E. The health endpoint driving the bands for those three chemicals were primarily STOT-RE and cancer.

Of the 4 chemicals for which the OEL corresponded to band A, the reviewers tended to band the chemicals in more protective bands. None of the reviewers placed the chemicals in band A. The health endpoints driving these decisions appeared to be reproductive toxicity data in one case and STOT-RE, sensitization or irritation for the remainder. This may reflect the presence of more recent toxicity data than that which supported the OELs or the banding criteria may weight certain data types, such as irritation and sensitization data differently than an OEL setting process. In any case, the bands selected in the banding process for these chemicals were more protective than the OELs.

It is important to understand which endpoints drive the final band in order to assess whether the banding criteria is appropriate. There is higher confidence when the banding relies on the more quantitative endpoints, such as carcinogenicity, reproductive toxicity and STOT-RE. For the chemicals in this analysis, at times the band corresponding to the OEL suggested lower toxicity than the Tier 2 banding process. In those cases, frequently the band was supported by carcinogenicity data, reproductive toxicity data or data from STOT-RE. In those cases, rather than overprotection of the banding process, it may suggest that the OELs is under-protective for those endpoints. This may be the result of OELs set many years ago using different data or criteria than are accessible today. Further research on this point is warranted.

With regard to inter-user variability, there remains some variability in application of the banding process. Comparison of the banding results supports earlier analyses indicating that the acute toxicity, carcinogenicity and reproductive endpoints had the highest number of matches, while reviewers disagreed more frequently about genotoxicity data, eye-irritation and corrosion, and skin irritation and corrosion. When comparing Tier 2 bands to exiting OELs for the 20 chemicals, all but one chemical is more protective than existing OELS.

Figure 6-7: Tier 2 Occupational Exposure Banding Results for 20 Chemicals (2 reviewers each) Compared to Their Minimum OEL



Discussion of Tier 2 Evaluation

Since 2014, NIOSH has conducted a number of evaluation exercises to evaluate interrater reliability and overall agreement of the OEB methodology as well as refine the descriptions of the methodology in this document. A detailed analysis of the individual evaluations have been described above. A summary of evaluation activities primarily focusing on Tier 2 is presented in Table 6-5.

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-14	Sep-14	Jun-15	Sep-15	Oct-16
Purpose	To prototype training and conduct preliminary interrater reliability.	To conduct large scale banding effort and refine process.	To review endpoints results with interrater reliability.	To obtain additional data on Tier 2 endpoints to determine level of detail within endpoint descriptions.	To assess accuracy and usability across chemicals for additional chemicals.
NIOSH Training class completed	Yes	Yes	Yes	Yes	Yes
Number of chemicals	10	102	3	3	20
Number of chemicals 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 that had lesser quality.	Some endpoints such as skin sensitization needed more information.	Recruitment was easy, it was difficult to obtain completed information from reviewers. Learning curve was significant.	Confusion on TDS scoring in some cases.	Good agreement with endpoints based upon quantitative data.
How OEB Methodology or Document Refined?	Data sources curtailed to insure data quality	Materials with key sources were created. Skin sensitization endpoint documentation re-written.	Genotoxicity endpoint description was rewritten. Training on Tier 2 re-designed with example	TDS was streamlined and enhanced for clarity.	Endpoints based upon qualitative endpoints such as genotoxicity were further refined to aid in users finding information sources

When analyzing the evaluation phases, key points can be identified as shown in Table 6-5. Other salient factors have also been highlighted which will be critical to OEB dissemination activities in the future. Users of Tier 2 must be well trained in how to use the NIOSH process. Discrepancies between users in selecting endpoint bands seem to be related to ability to locate data. In response, NIOSH has clarified the instructions to ameliorate this issue. Additionally, NIOSH has developed a training class with blended learning opportunities and is drafting a toxicology primer with skill-check questions to aid the process. This will better prepare users to understand the endpoints.

The Tier 2 criteria operated as expected and the resulting bands showed overall consistency. Completing a Tier 2 evaluation requires substantial effort, not unlike other decision logics in occupational hygiene. Reviewers reported that banding a single chemical required hours to days. But this amount of time and effort is substantially less that what is required for a full quantitative risk assessment. The variability in TDS scores reflects that reviewers 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 chemicals of interest.

For some endpoints, variability in the endpoint specific band between users existed. The variability in some endpoints appeared related to the clarity of the instructions and ease of use of the criteria. It is important that users read the occupational exposure banding process in its entirety before attempting to band chemicals. Compliance with this 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, and this created problems for users and is reflected in variability in the banding. This points to a need for a more streamlined and usable process. Given these observations, the guidance document was streamlined to enhance usability. In addition, an online tool is available to help facilitate the occupational exposure banding process. After each evaluation phase, enhancements have been made to the occupational exposure banding documentation and training materials, thereby improving the methodology. This process will continue as the document undergoes both external peer review, public and stakeholder comment.

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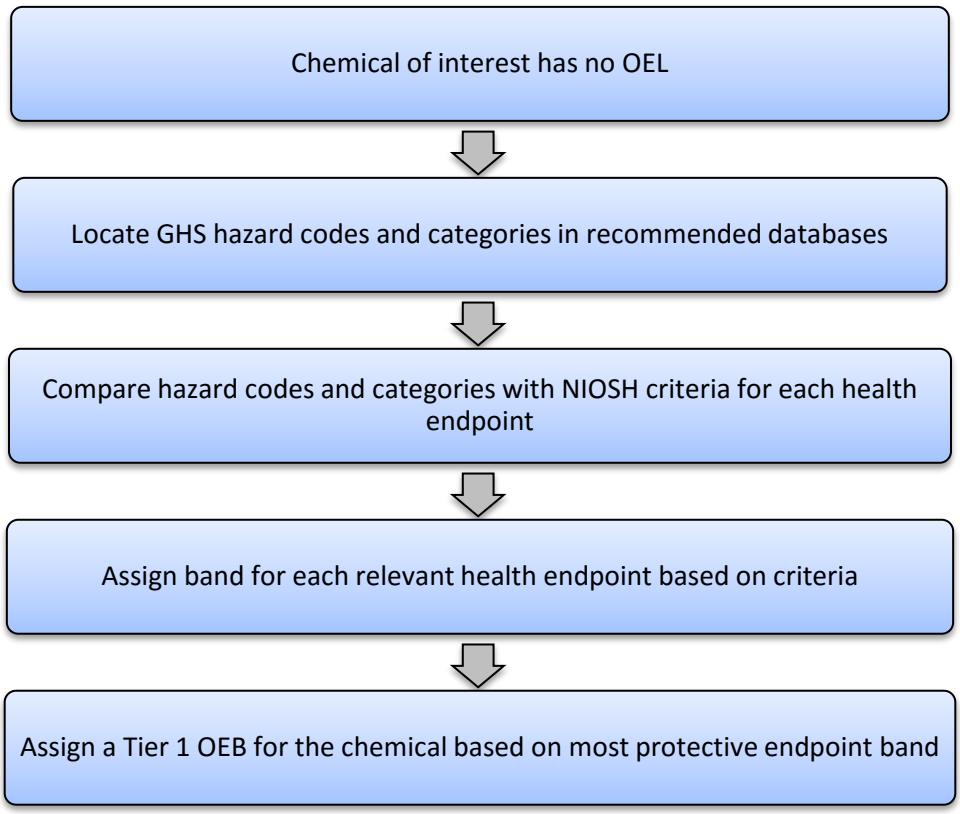
Appendix A: Helpful Information for Banding Chemicals in Tier 1

This Appendix provides supplemental information needed to band chemicals in Tier 1. Section A.1 gives a brief overview of the Tier 1 banding process. Section A.2 provides the NIOSH Tier 1 banding criteria. Once users gather the hazard codes and hazard categories necessary to complete Tier 1, they can then compare this data to the NIOSH criteria to determine an endpoint specific band. Hazard codes and categories can be retrieved from the GESTIS Substance Database, the Annex VI database, or a reliable OSHA-compliant SDS. Section A.3 provides the worksheet that can be filled out to keep a record of 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 Tier 1 banding process.

Section A.1 Tier 1 overview

Tier 1 Overview



Section A.2 Tier 1 Criteria Overview: GHS Hazard Codes and Categories for Tier 1

Preliminary NIOSH Tier 1 criteria		C	D	E
OEL ranges	Particle	> 0.1 to ≤ 1 milligrams per cubic meter of air (mg/m^3)	> 0.01 to ≤ 0.1 mg/m^3	≤ 0.01 mg/m^3
	Vapor	> 1 to ≤ 10 parts per million (ppm)	> 0.1 to ≤ 1 ppm	≤ 0.1 ppm
Acute toxicity		H301 Category 3 H302 Category 4 H331 Category 3 H332 Category 4 H311 Category 3 H312 Category 4	H300 Category 2 H330 Category 2 H310 Category 2	H300 Category 1 H330 Category 1 H310 Category 1
Skin corrosion/ irritation		H315 Category 2	—	H314 Category 1, 1A, 1B, or 1C
Serious eye damage/ eye irritation		H319 Category 2, 2A or 2B	—	H318 Category 1
Respiratory and skin sensitization		H317 Category 1B (skin) —	H317 Category 1 or 1A H334 Category1B	— H334 Category 1 or 1A
Germ cell mutagenicity		—	H341 Category 2	H340 Category 1, 1A or 1B
Carcinogenicity		—	—	H350 Category 1, 1A, or 1B H351 Category 2
Reproductive Toxicity		H361 *(including H361f, H361d, and H361fd)* Category 2	H360 *(including H360f, H360d, and H360fd)* Category 1B	H360 *(including H360f, H360d, and H360fd)* Category 1 or 1A
Specific target organ toxicity		H371 Category 2 H373 Category 2	—	H370 Category 1 H372 Category 1

Note that the following hazard codes will not be used for Tier 1 Banding: H200's, H303, H305, H313, H316, H320, H333, H335, H336, H362, and H400's.

Section A.3 Tier 1 Worksheet

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

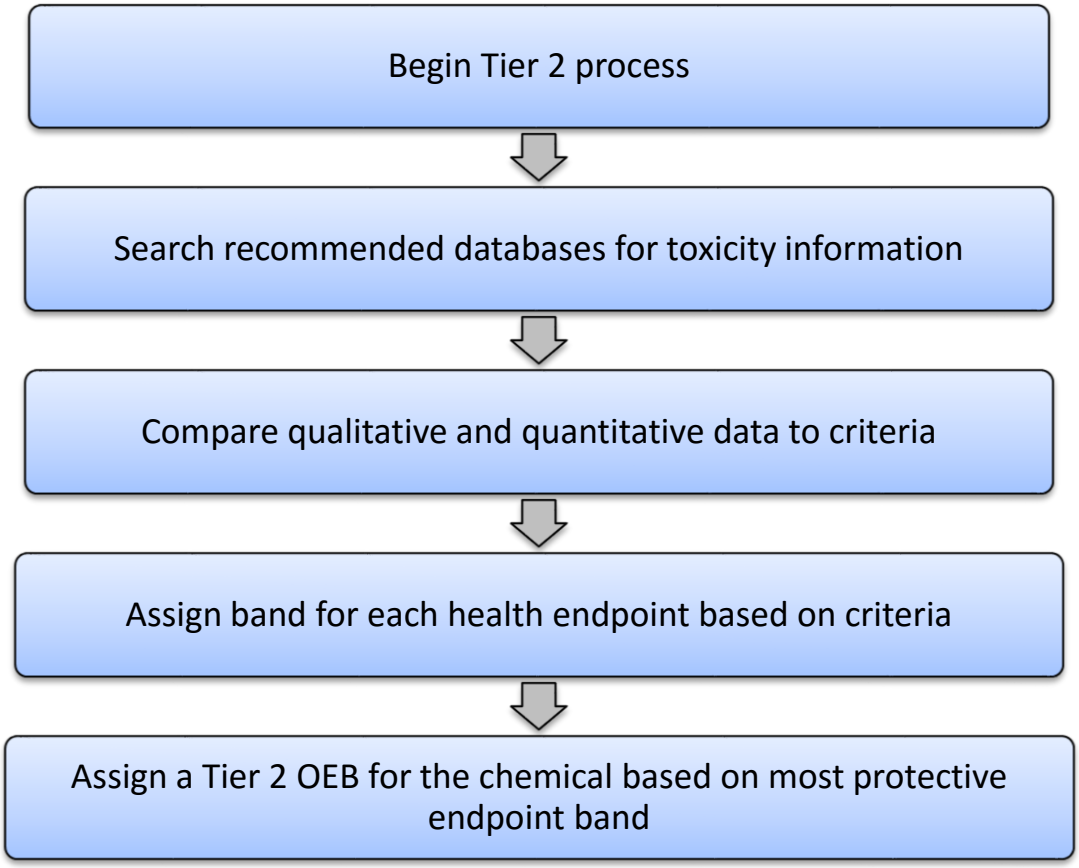
Chemical Name: **CAS:**					
Endpoint		**Hazard Code**	**Hazard Category**	**H-code Source**	**Endpoint Band**
Acute Toxicity	**Inhalation**				
	Oral				
	Dermal				
Skin Corrosion/Irritation					
Eye Damage/Eye Irritation					
Respiratory and Skin Sensitization					
Germ Cell Mutagenicity					
Carcinogenicity					
Reproductive Toxicity					
Specific Target Organ Toxicity					
Most Protective Tier 1 Band					

Notes:

Appendix B: Helpful Information for Banding Chemicals in Tier 2

This appendix provides supplemental information on banding chemicals in Tier 2. Section B.1 provides a brief overview of the Tier 2 banding process. Section B.2 provides a list of the assigned scores for each of the nine toxicological endpoints encountered in Tier 2 to determine the TDS. Section B.3 provides a list of recommended data sources for each of the nine endpoints. Section B.4 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 one endpoint at a time. Section B.5 provides a checklist that can be used to highlight the data that has been collected for each specific endpoint. A web tool is also available to assist with this process: https://www.cdc.gov/niosh/topics/oeb/default.html. Refer to Chapter 2 for more specific details on Tier 2 banding process.

Section B.1 Tier 2 Overview



Section B.2 Total Determinant Score: Assigned Scores for the Presence of Toxicological Endpoints Encountered in the Tier 2 Evaluation

Toxicological Endpoint	**Endpoint Determinant Score (EDS)**
Skin Irritation/Corrosion	5
Eye Irritation/Corrosion	5
Skin Sensitization	5
Acute Toxicity/Lethality (LD_{50} or LC_{50})	5
Genotoxicity	5
Respiratory Sensitization	10
Systemic Target Organ Toxicity (STOT-RE)	30
Reproductive and Developmental Toxicity	30
Cancer WOE	20 or 30
Cancer SF, IUR, or TD/TC_{05} (Health Canada)	30
Endpoint Determinant Score for Cancer	20 or 30
Data Sufficiency/Total Determinant Score (TDS)	30/125

Section B.3 Data 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 [Canada 1996]	HC
		State of California Office of Environmental Health Hazard Assessment [CAL/EPA 2010]	Cal OEHHA
Reproductive toxicity	1	U.S. National Toxicology Program [NTP 2016]	NTP
		Health Canada [Canada 1996]	HC
		California Environmental Protection Agency [CAL/EPA 2016]	CalEPA
		Agency for Toxic Substances & 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]	U.S. EPA RED
		European Chemicals Agency; Registration, Evaluation, Authorisation and Restriction of Chemicals [ECHA 2016]	ECHA; REACH
Specific Target Organ Toxicity (STOT-RE)	1	Agency for Toxic Substances & 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 [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
Genotoxicity	1	U.S. National Toxicology Program [NTP 2016]	NTP
		Agency for Toxic Substances & 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 & 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
Acute Toxicity	1	National Library of Medicine ChemID Plus [ChemID 2016]	ChemID Plus
		U.S. EPA Superfund Chemical Data Matrix [EPA 2016b]	U.S. 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 & Disease Registry Toxicological Profiles [ATSDR 2016]	ATSDR
	1	NIOSH Skin Notation Profiles [NIOSH 2009b]	SK Profiles
		World Health Organization International Programme on Chemical Safety [WHO-IPCS 2015]	WHO-IPCS

Skin Irritation/Skin Corrosion		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
Serious Eye Damage/Eye 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 & Disease Registry Toxicological Profiles [ATSDR 2016]	ATSDR
		U.S. EPA Integrated Risk Information System [EPA 2014]	IRIS

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

Section B.4 Endpoint Specific Criteria for Banding

Cancer

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 **Cancer**			
Exposure/ Dosing Route	**Band**		
	C	**D**	**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	$< 3 \times 10^{-6}$ (µg/m^3)$^{-1}$	$\geq 3 \times 10^{-6}$ 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}	> 16700 µg/m^3	> 5 to ≤ 16700 µg/m^3	≤ 5 µg/m^3

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**

1 Worksheet for Cancer

Carcinogenicity (20 or 30 points possible)				
	Band A	**Band C**	**Band D**	**Band E**
NTP/EPA/IARC/Canada/California (QUALITATIVE)				
EPA IRIS Slope Factor				
EPA IRIS Inhalation Unit Risk				
Health Canada TD05				
Health Canada TC05				
California Slope Factor				
California Inhalation Unit Risk				

2

3

4

5

6

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 & 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	U.S. EPA RED
		European Chemicals Agency; Registration, Evaluation, Authorisation and Restriction of Chemicals	ECHA; REACH

Criteria for Reproductive Toxicity Endpoint

NIOSH Banding Criteria for **Reproductive Toxicity** (NOAEL/BMDL/BMCL)					
Exposure/ Dosing Route	**Band**				
	A	**B**	**C**	**D**	**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 and vapors)	> 10,000 ppm	> 1,000 to ≤10,000 ppm	> 100 to ≤1,000 ppm	> 10 to ≤100 ppm	≤10 ppm
Inhalation (dusts and mists)	> 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

Worksheet for Reproductive Toxicity

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

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 & 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

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

NIOSH Banding Criteria for **Specific Target Organ Toxicity** (NOAEL/BMDL)					
Exposure/ Dosing Route	**Band**				
	A	**B**	**C**	**D**	**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 (dusts and mists)	>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 and 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.*

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

Specific Target Organ Toxicity (STOT-RE) (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 & 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	**C**	**E**
Negative Results	Mixed results	Positive Results

Worksheet for Genotoxicity

Genotoxicity (5 points possible)			
Data supports:	**Negative Results (Band A)**	**Mixed Results (Band C)**	**Positive Results (Band E)**
If data available, put data 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 & 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	**C**	**E**
No evidence of respiratory sensitization	Mixed results	Positive evidence of respiratory sensitization

Worksheet for Respiratory Sensitization Endpoint

Respiratory sensitization (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 data 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

Criteria for Skin Sensitization Endpoint

NIOSH Banding Criteria for **Skin Sensitization**			
Test Type	**Band**		
	A	**C**	**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
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

Worksheet for Skin Sensitization

Skin sensitization (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:			

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	U.S. 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 & Disease Registry	ATSDR

Criteria for Acute Toxicity Endpoint

NIOSH banding criteria for **Acute Toxicity**					
Exposure/Dosing Route	**Band**				
	A	**B**	**C**	**D**	**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 (LC_{50})	> 20,000 ppmV/4h	>2,500 to ≤ 20,000 ppmV/4h	>500 to ≤ 2,500 ppmV/4h	>100 to ≤ 500 ppmV/4h	≤ 100 ppmV/4h
Inhalation vapors (LC_{50})	> 20.0 mg/liter/4h	>10.0 to ≤ 20.0 mg/liter/4h	>2.0 to ≤ 10.0 mg/liter/4h	>0.5 to ≤ 2.0 mg/liter/4h	≤ 0.5 mg/liter/4h
Inhalation dusts and mists (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

Worksheet for Acute Toxicity

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

***If multiple LD50 or LC50 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 & Disease Registry	ATSDR
		U.S. EPA Integrated Risk Information System	IRIS

Criteria for Skin Corrosion/Irritation Endpoint

NIOSH Banding Criteria for **Skin Irritation/Skin Corrosion**			
Band			
A	**B**	**C**	**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 irritation/corrosion (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 if 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 data in this row corresponding to the correct band criteria; otherwise leave blank.				
Source, Rank 1 or 2:				

Eye Damage/Eye Irritation

Data Sources

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 & Disease Registry	ATSDR
		U.S. EPA Integrated Risk Information System	IRIS

Criteria for Eye Damage/Eye Irritation Endpoint

NIOSH Banding Criteria for **Serious Eye Damage/Eye Irritation**			
Band			
A	**B**	**C**	**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

Worksheet for Eye Damage/Eye Irritation

Eye damage/Eye irritation (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 data in this row corresponding to the correct band criteria; otherwise leave blank.				
Source, Rank 1 or 2:				

Section B.5 Full Table for Tier 2 Hazard Banding

If using the electronic version of this spreadsheet, 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. A check mark should be inserted in the appropriate column for each row of data. The determinant score for each health endpoint/toxicity parameter should be calculated in the determinant score column. The most protective of all the bands entered is the final Tier 2 OEB for the chemical.

Chemical Name: **CAS:**			
Endpoint	**Data**	**EDS**	**Endpoint Band**
Acute Toxicity	Source:		
Skin Corrosion/Irritation	Source:		
Serious Eye Damage/ Eye Irritation	Source:		
Respiratory Sensitization	Source:		
Skin Sensitization	Source:		
Genotoxicity	Source:		
Carcinogenicity	Source:		
Reproductive Toxicity	Source:		
Specific Target Organ Toxicity	Source:		
OVERALL Tier 2 BAND		**TDS=**	

Appendix C: Examples of Chemicals Banded in Tier 1

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

Chemical Name: Bentazone

Chemical Name: Bentazone CAS: 25057-89-0					
Endpoint		**Hazard Code**	**Hazard Category**	**H-code source**	**Endpoint Band**
Acute Toxicity	**Inhalation**				C
	Oral	H302	Category 4	GHS	
	Dermal				
Skin Corrosion/Irritation					
Serious Eye Damage/ Eye Irritation		H319	Category 2	GHS	C
Respiratory and Skin Sensitization		H317	Category 1	GHS	C
Germ Cell Mutagenicity					
Carcinogenicity					
Reproductive Toxicity					
Specific Target Organ Toxicity					
Most Protective Band					**C**

Result:

Band C is assigned as a result of the Tier 1 evaluation. A Tier 2 evaluation is recommended.

Chemical Name: Perfluorooctane Sulfonic Acid

Chemical Name: Perfluorooctane Sulfonic Acid CAS: 1763-23-1					
Endpoint		**Hazard Code**	**Hazard Category**	**H-code Source**	**Endpoint Band**
Acute Toxicity	**Inhalation**	H332	Category 4	GHS	C
	Oral	H302	Category 4	GHS	
	Dermal				
Skin Corrosion/Irritation		H314	Category 1B	GHS	E
Eye Damage/Eye Irritation					
Respiratory and Skin Sensitization					
Germ Cell Mutagenicity					
Carcinogenicity		H351	Category 2	GHS	E
Reproductive Toxicity		H360D	Category 1B	GHS	D
Specific Target Organ Toxicity		H372	Category 1	GHS	E
Most Protective Band					**E**

Result:

Band E is assigned as a result of the Tier 1 evaluation. A Tier 2 evaluation is optional.

Appendix D: Example of Chemical Banded in Tier 2

This appendix provides an example of a chemical NIOSH has banded by using 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. The completed worksheet for the relevant health endpoints follow:

Carcinogenicity (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 carcinogenicity in animals.
EPA IRIS Slope Factor					
EPA IRIS Inhalation Unit Risk					
Health Canada TD05					
Health Canada TC05					
California Slope Factor				$1.2\ (mg/kg\text{-}day)^{-1}$	
California Inhalation Unit Risk				$1.1x10^{-4}\ (ug/m^3)^{-1}$	

- Cancer data was retrieved from EPA IRIS and CalOEHHA 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 (5 points possible)			
Data supports:	**Negative Results (Band A)**	**Mixed Results (Band C)**	**Positive Results (Band E)**
If data available, put data 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 irritation/corrosion (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 if 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 data 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 is assigned, and a determinant score of 5 is assigned.

Eye irritation/corrosion (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)**	**Serious or irreversible eye damage (E)**
If data available, put data in this row corresponding to the correct band criteria; otherwise leave blank.			Irritation and photosensitivity described. No indication of severity.	
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 is calculated. This TDS exceeds the threshold for data sufficiency (TDS≥30). The most protective band assigned is band E. The final Tier 2 band for benzo (k) fluoranthene is band E, on the basis of genotoxicity.

Appendix E: Chemicals

The following is a list of chemicals used for the evaluation exercises described in Chapter 6.

1. Potassium Bromate
2. Mancozeb
3. Nitrochlorobenzene p-
4. Nitroaniline p-
5. Terephthalic acid
6. Dinitrobenzene p-
7. Diethylaminoethanol 2-
8. Vinylcyclohexene
9. Ethyl benzene
10. Styrene - monomer
11. Benzyl chloride
12. Benzyl Alcohol
13. Benzaldehyde
14. Methyl aniline N-
15. Phenylhydrazine
16. Ethylmorpholine N-
17. Nitrous oxide
18. Sulfur monochloride
19. Phosphorus oxychloride
20. Phosphorus pentachloride
21. Ozone - Heavy work
22. Hydrogen bromide
23. Chlorine dioxide
24. Methylene bisphenyl isocyanate [MDI]
25. Methylene dianiline 4,4'-
26. Phenyl ether - Vapor
27. Nitric oxide
28. Nitrogen dioxide
29. Dicyclopentadienyl iron
30. Triethanolamine
31. Dibutylaminoethanol 2-N-
32. Cobalt carbonyl (as Co)
33. Barium chromate (as Cr)
34. Ethylhexanol 2-
35. Anisidine p-
36. Butyl acetate sec-
37. Caprolactam - Vapor
38. Ethyl butyl ketone
39. Xylene p-
40. Cresol p-
41. Dichlorobenzene p-
42. Toluidine p-
43. Phenylenediamine p-
44. Quinone
45. Vinyl cyclohexene dioxide
46. 1,2-Epoxybutane
47. Epichlorohydrin
48. Glycidyl Methacrylate
49. Allyl glycidyl ether
50. Ethylene dibromide
51. Propargyl Bromide
52. Butane
53. Butadiene 1,3-
54. Allyl chloride
55. Ethylene dichloride
56. Ethylene chlorohydrin
57. Propionitrile
58. Acrylonitrile
59. Ethylenediamine
60. Allyl alcohol
61. Propargyl alcohol
62. Ethylene glycol
63. Glyoxal
64. Methyl formate
65. Hexylene glycol
66. TEPP [Tetraethyl pyrophosphate]
67. Dibutyl phosphate
68. Methyl pentane 2-
69. Methyl propyl ketone
70. Methoxy-2-propanol [PGME] 1-
71. Nitropropane 1-
72. Vinyl acetate
73. Methyl isobutyl ketone
74. Methyl isobutyl carbinol
75. Diisopropylamine
76. Isopropyl ether
77. Isopropyl acetate
78. Acetic anhydride
79. Maleic anhydride
80. Xylene m-
81. Cresol m-
82. Toluidine m-
83. Phenylenediamine m-
84. Resorcinol
85. Propylene Glycol Monomethyl Ether Acetate
86. Trimethyl benzene [Mesitylene] 1,3,5-
87. Trichlorobenzene 1,3,5-
88. Melamine
89. Isocyanuric Acid
90. Diisobutyl ketone
91. Hexyl acetate sec-
92. Methylcyclohexane
93. Toluene
94. 4-Picoline
95. Chlorobenzene
96. Cyclohexylamine
97. Cyclohexanol
98. Cyclohexanone
99. Phenol
100. Phenyl mercaptan
101. 3-Picoline
102. 2-Picoline

103. Isopropoxyethanol 2-
104. Propyl acetate n-
105. Pentane n-
106. Butylamine n-
107. Malononitrile
108. Butyl mercaptan n-
109. Methoxyethanol 2-
110. Methylal
111. Diethylamine
112. Ethyl formate
113. Tetrahydrofuran
114. Methyl isoamyl ketone
115. Isobutyl acetate
116. Methyl n-amyl ketone
117. Methoxyethyl acetate 2-
118. Hexane n-
119. Succinonitrile
120. Valeraldehyde n-
121. Ethoxyethanol [EGEE] 2-
122. Cyclohexane
123. Cyclohexene
124. Pyridine
125. Piperidine
126. Morpholine
127. Chlorodiphenyl (54% chloride)
128. Nickel oxide
129. Ethoxyethyl acetate [EGEEA] 2-
130. n-Hexyl Alcohol
131. Glutaraldehyde
132. Diethylene triamine
133. Diethanolamine
134. Dichloroethyl ether
135. Diethylene Glycol
136. Octane n-
137. 1-Octene
138. Adiponitrile
139. Butoxyethanol 2-
140. Nonane - All isomers
141. 1-Octanol
142. Diethylene Glycol Monoethyl Ether
143. Methoxyethyl)ether bis(2-
144. Zinc potassium chromate (as Cr)
145. Butoxyethyl acetate 2-
146. Triethylenetetramine
147. Butoxyethoxy)ethanol 2-(2-
148. TetraethylenePentamine
149. Silica, Amorphous -- Precipitated and gel
150. Erythromycin
151. Propoxur
152. Dimethyl Ether
153. Endosulfan
154. Pentaerythritol
155. Triphenyl phosphate
156. Fensulfothion
157. Aldicarb
158. Tetrafluoroethylene
159. Decabromodiphenyl Oxide
160. Di(2-ethylhexyl)phthalate [DEHP]
161. Dichloro-5,5-dimethyl hydantoin 1,3-
162. Hexachlorobenzene [HCB]
163. Trinitrotoluene [TNT] 2,4,6-
164. Butyl chromate (as CrO_3) tert-
165. Benzophenone
166. Dimethyl Terephthalate
167. Catechol
168. 2,4-Dichlorophenol
169. Mica
170. Trichlorobenzene - All isomers
171. Nickel dioxide
172. Nickel subsulfide (as Ni)
173. Nickelous hydroxide (as Ni)
174. Tungsten carbide - Containing > 2% cobalt, as Co
175. Manganese cyclopentadienyl tricarbonyl (as Mn)
176. Dinitrotoluene 2,4-
177. Vanillin
178. Triethylamine
179. Trimethyl phosphite
180. Dimethylaniline
181. Malathion
182. Cyclonite
183. Isophthalic Acid
184. Methylcyclopentadienyl manganese tricarbonyl 2-
185. Ammonium chloride - Fume
186. Borates, tetra, sodium salts, Pentahydrate
187. Diphenylamine
188. Phenyl glycidyl ether [PGE]
189. Phenoxyethanol 2-
190. Dipropyl ketone
191. Hydroquinone
192. Butylated hydroxytoluene [BHT] - Vapor & Aerosol
193. Propionaldehyde
194. Diacetone alcohol
195. Isoamyl alcohol
196. Butyraldehyde
197. Butyl acetate n-
198. Dioxane 1,4-
199. Isopentyl acetate
200. Diallylamine
201. Adipic acid
202. 1,6-Hexanediamine
203. Carbon dioxide
204. Dimethylamine
205. Tributyl phosphate

206. Methylacrylonitrile
207. beta-Chloroprene
208. Ferrovanadium - dust
209. Chloro-2-propanol 1-
210. Tetrachloroethylene [Perchloroethylene]
211. Dimethylacetamide N,N-
212. Emery
213. Gallium arsenide
214. Arsenic pentoxide (as As)
215. Boron oxide
216. Borates, tetra, sodium salts, Decahydrate
217. Bismuth telluride - Undoped
218. Hexanediol Diacrylate
219. Calcium hydroxide
220. Calcium oxide
221. Terbufos - Vapor & aerosol
222. Iron oxide [Fe_2O_3] - dust (as Fe)
223. Magnesium oxide - Fume
224. Antimony trioxide (as Sb)
225. Dimethyl phthalate
226. Sodium hydroxide
227. Cyhexatin
228. Nickel sesquioxide
229. Zinc oxide - Dust
230. Phosphorus pentoxide
231. Tantalum oxide - Dust (as Ta)
232. Vanadium pentoxide - Fume (as V_2O_5)
233. Phosphorus pentasulfide
234. Manganese tetroxide (as Mn)
235. Silica, Crystalline -- Tripoli
236. Cresol - mixture of isomers
237. Pentachloronaphthalene
238. Trichloronaphthalene
239. Divinyl benzene
240. Captan
241. Xylene - Mixed isomers
242. Borates, tetra, sodium salts, Anhydrous
243. Xylidine - Mixed isomers (Vapor & aerosol)
244. Kaolin
245. Carbon black
246. Hexachloronaphthalene
247. Tetrachloronaphthalene
248. Methyl ethyl ketone peroxide [MEKP]
249. Gypsum
250. Aluminum oxide
251. Calcium silicate - Synthetic
252. Nickel carbonyl (as Ni)
253. Iron pentacarbonyl
254. Tellurium - Compounds (as Te)
255. Zinc chromate (as Cr)
256. Sesone
257. Methyl 2-cyanoacrylate
258. Thiram
259. Calcium chromate (as Cr)
260. Butyl lactate n-
261. d-Limonene
262. Enflurane
263. Subtilisins [Proteolytic enzymes]
264. Butylamine sec-
265. Benzyl acetate
266. Ethyl acrylate
267. Butyl acrylate n-
268. Ethanolamine
269. Dicrotophos - Vapor & Aerosol
270. Ethyl acetate
271. Mesityl oxide
272. Piperazine dihydrochloride
273. Heptane n-
274. Sodium cyanide (as CN)
275. Chlordecone
276. Oxalic acid
277. Silica, Crystalline -- Cristobalite
278. Ferbam
279. Tri-n-butyltin chloride (as TBTO)
280. m-Xylene alpha,alpha'-diamine
281. Dinitolmide
282. Sodium diethyldithiocarbamate
283. Talc - Containing no asbestos fibers
284. Silica, Crystalline -- Quartz
285. Dimethylethoxysilane
286. 2-Mercaptobenzothiazole
287. Ethylhexanoic acid - Vapor & aerosol 2-
288. para-Aminobenzoic Acid
289. Methoxyphenol 4-
290. Potassium cyanide (as CN)
291. Ethylenimine
292. Halothane
293. Silica, Crystalline -- Tridymite
294. Dichloroethylene, cis-isomer 1-2
295. Dichloroethylene, trans-isomer 1,2-
296. Calcium cyanamide
297. TrimethylolpropaneTriacrylate
298. Carbofuran
299. Methoxy-1-propanol 2-
300. Butanol (+/-)-2-
301. Sodium pyridinethione
302. Methyl tert-butyl ether [MTBE]
303. HFE-7100
304. HFE-7100

305. 1,3,3,3-Tetrafluoropropylene
306. Methomyl
307. Triethylene Glycol Diacrylate
308. Cobalt hydrocarbonyl (as Co)
309. 1,1-Dichloro-1-Fluoroethane
310. Decaborane
311. Benomyl
312. Tetraethylene Glycol Diacrylate
313. Tin dioxide (as Sn)
314. Paraquat dichloride
315. Atrazine
316. Picloram
317. Diborane
318. Nitrapyrin
319. Pentaborane
320. Tributyltin fluoride (as TBTO)
321. Benzenesulfonic acid, 5-chloro-2((2-Hydroxy-1-napthalenyl)-azo)-4-methyl, barium salt (2:1)
322. Chlorostyrene o-
323. Propoxyethyl acetate 2-
324. Paraquat dimethyl sulfate
325. Osmium tetroxide
326. EPN
327. Metribuzin
328. Cesium hydroxide
329. Tributyltin methacrylate (as TBTO)
330. Aluminum hydroxide
331. Stannous oxide (as Sn)
332. Allyl propyl disulfide
333. Chrysene
334. Fenamiphos
335. Nitrobutyl)morpholine 4-(2-
336. Octachloronaphthalene
337. Diglycidyl ether [DGE]
338. Methyl mercury (as Hg)
339. 2,3,5,6-Tetrachloropyridine
340. Tributyltin linoleate (as TBTO)
341. Captafol
342. Butyl glycidyl ether [BGE] n-
343. Triglycidyl-s-triazinetrione 1,3,5-
344. Trimethoxysilane
345. Vinyl toluene [Methyl styrene] - Mixed isomers
346. Diisobutylene
347. Dibutyl phenyl phosphate
348. Dinitrotoluene
349. Polyethylene Glycols (MW > 200)
350. Polypropylene Glycols
351. Diethylbenzenes,mixed isomers
352. 2,4-Toluene Diamine and mixed isomers
353. Sulfur hexafluoride
354. Methylcyclohexanol
355. Terphenyl - Mixed isomers
356. Chloro-2-methyl-2,3-dihydroisothiazol-3-one 5-
357. Plaster of Paris
358. Octyl-4-isothiazolin-3-one 2-
359. Sodium azide (as Sodium azide)
360. Isooctyl alcohol
361. Chlorobenzylidene malononitrile o-
362. Sulfuryl fluoride
363. Diquat
364. Propoxyethanol 2-
365. 2-Chloro-1,1,1,2-Tetrafluoroethane
366. Cyclopentane
367. Dehydrolinalool
368. Chlorpyrifos
369. 2-Propenoic Acid, Isooctyl Ester
370. Clopidol
371. Methyl parathion
372. Phorate
373. Disulfoton - Vapor & Aerosol
374. Ronnel [Fenchlorphos]
375. Crufomate
376. Naled - Vapor & aerosol
377. Hydrazine
378. Bis(2-dimethylaminoethyl) ether [DMAEE]
379. 1,1,1-Trifluoro-2,2-Dichloroethane
380. Aldrin
381. Chlorinated diphenyl oxide o-
382. Bromacil
383. Naphthalene diisocyanate [NDI]
384. Hexachlorocyclohexane alpha-
385. Hexachlorocyclohexane beta-
386. Trimethylolpropane Trimethacrylate
387. Dibromoneopentyl Glycol
388. Diuron
389. Diazinon
390. Tetramethyl succinonitrile
391. Nickelous carbonate
392. Diazomethane
393. Temephos
394. Methoxypropyl) ether [DPGME] bis, (2-
395. Pentaerythritol Triacrylate
396. Carbonyl fluoride
397. 1,1,1,2,2-Pentafluoroethane
398. Sulprofos
399. Lead arsenate (as As)
400. Sulfotep [TEDP]

401. Zinc yellow (as Cr)
402. 2-Phosphono-1,2,4 butanetricarboxylic acid
403. Sodium pyrithione
404. Ammonium perfluorooctanoate
405. Sodium Chloroacetate
406. Zinc beryllium silicate (as Be)
407. bis-(2-Chloroisopropyl)Ether
408. Isopropyl glycidyl ether [IGE]
409. Silicon carbide
410. Isophorone diisocyanate
411. Crotonaldehyde
412. Cyanamide
413. 1,1,1-Trifluoroethane
414. Tributyl tin benzoate (as TBTO)
415. Cyanogen
416. 1,1,1,3,3-Pentafluoropropane
417. Ketene
418. tert-Pentane [Neopentane]
419. Paraquat
420. Calcium carbonate
421. Tetryl
422. Formaldehyde
423. DDT [Dichlorodiphenyltrichloroethane]
424. Benzo[a]pyrene
425. Acetylsalicylic acid
426. Aminopyridine 2-
427. Tetranitromethane
428. Methylene bis(4-cyclohexylisocyanate)
429. Trimethyl benzene 1,2,3-
430. Dinitrobenzene o-
431. Chloroacetophenone 2-
432. 3-Methoxypropylamine
433. Dinitro-o-cresol
434. Chlorodiphenyl (42% chloride)
435. Nicotine
436. Thimerosal
437. Dichloroethylene, sym-isomer 1-2
438. Isooctane
439. Butyl acetate tert-
440. Ethyl amyl ketone
441. Dichloropropene 1,3-
442. Chloromethyl) ether bis
443. Cyclopentadiene
444. Magnesite
445. Fenthion
446. Nitroglycerin [NG]
447. Trimellitic anhydride
448. Glycidol
449. Zinc stearate
450. Carbon tetrabromide
451. Carbon tetrachloride
452. Tri-n-butyltin)oxide [TBTO] (as TBTO) bis(
453. Parathion
454. Chloramphenicol
455. Glycerin - mist
456. Ethion
457. Methyl isopropyl ketone
458. Urea
459. Dimethylhydrazine 1,1-
460. Strychnine
461. Sucrose
462. Propylene Glycol
463. Propiolactone beta-
464. Chlordane
465. Sulfur pentafluoride
466. Lindane
467. Methylcyclohexanone o-
468. Toluene-2,4-diisocyanate [2,4-TDI]
469. Methyl n-butyl ketone
470. Calcium cyanide (as CN)
471. Hexene 1-
472. 1,4-Hexadiene
473. Vinyl bromide
474. Methyl acetylene-propadiene mixture [MAPP]
475. Perchloromethyl mercaptan
476. Dichloro-1-nitroethane 1,1-
477. Dimethyl ethylamine N,N-
478. Chloropropionic acid 2-
479. Mercaptoethanol
480. Ethyl ether
481. Methyl hydrazine
482. Dieldrin
483. Chloro-1-nitropropane 1-
484. Triphenyl amine
485. Silica, Amorphous -- Fused
486. Amitrole
487. Dowtherm Q
488. Hydrogenated terphenyls - Nonirradiated
489. Silica, Amorphus - Diatomaceous Earth (uncalcined
490. Dinitrotoluene 3,5-
491. Aniline
492. Dichlorvos [DDVP] - Vapor & Aerosol
493. Sodium fluoroacetate
494. Pentyl acetate 3-
495. Methylbutyl acetate 2-
496. Methyl isocyanate
497. Pentyl acetate tert-
498. Methoxyacetic acid
499. Phthalodinitrile m-
500. Pentyl acetate 2-
501. Propyl nitrate n-
502. Pentyl acetate 1-
503. HexamethyleneGlycol
504. Carbaryl
505. Carbon monoxide

506. Ethyl tert-butyl ether [ETBE]
507. Ethanol
508. Formic acid
509. Acetic acid
510. Aminotri (Methylenephosphonic Acid)
511. Propylene glycol dinitrate
512. Dioxolane 1,3-
513. Coal tar pitch volatiles-as benzene-sol. Aerosol
514. Portland cement
515. Methanol
516. Isopropanol [Isopropyl alcohol]
517. Acetone
518. Chloroform
519. Dimethyl Sulfoxide
520. Hexachloroethane
521. Thioglycolic acid
522. Dimethylformamide
523. Methyl silicate
524. Diesel fuel - Vapor & aerosol
525. Hexafluoroacetone
526. Diesel fuel No. 2 - Vapor & aerosol
527. Liquified petroleum gas [L.P.G.]
528. Silica, Amorphous - Diatomaceous earth (calcined)
529. Dowtherm Q
530. 1,1,1,3,3,3-Hexafluoropropane
531. Monocrotophos - Vapor & Aerosol
532. Heptachlor epoxide
533. Methoxy-1-propyl acetate 2-
534. Ethyl cyanoacrylate
535. Propanol n-
536. Butanol n-
537. n-Amyl Alcohol
538. Benzene
539. Methyl chloroform
540. Endrin
541. Methoxychlor
542. Methyl bromide
543. Methyl chloride
544. Methyl iodide
545. Methylamine
546. Hydrogen cyanide (as CN)
547. Methyl mercaptan
548. Ethyl bromide
549. Chlorobromomethane
550. Propane
551. Methyl acetylene
552. Sulfometuron methyl
553. Aluminum - Metal dust
554. Lead - elemental and inorganic compounds (as Pb)
555. Manganese - Elemental & inorganic cmpds (as Mn)
556. Mercury - Alkyl compounds (as Hg)
557. Molybdenum - Soluble compounds (as Mo)
558. Nickel - Soluble inorganic compounds (as Ni)
559. Platinum - Metal
560. Rhodium - Soluble compounds (as Rh)
561. Silicon
562. Silver - Soluble compounds (as Ag)
563. Tantalum - Metal
564. Thallium - Soluble compounds (as Tl)
565. Tin - Metal
566. Tin - Organic compounds (as Sn)
567. Tungsten - Insoluble compounds (as W)
568. Antimony - Compounds (as Sb)
569. Arsenic - Elemental
570. Barium - Soluble compounds (as Ba)
571. Beryllium - Compounds (as Be)
572. Cadmium - Metal & compounds (as Cd)
573. Graphite
574. Chromium (VI) compounds (as Cr)
575. Cobalt - Elemental / Metal
576. Copper - Fume (as Cu)
577. Hafnium and compounds, as Hf
578. Uranium (Natural) - Insoluble compounds (as U)
579. Yttrium - Compounds (as Y)
580. Zirconium - Compounds (as Zr)
581. Indium and compounds (as In)
582. Sulfur dioxide
583. Lead phosphate (as Pb)
584. Selenium sulfide (as Se)
585. Ethyl chloride
586. Vinyl chloride
587. Vinyl fluoride
588. Ethylamine
589. Acetonitrile
590. Acetaldehyde
591. Ethyl mercaptan
592. Dichloromethane
593. Difluoromethane
594. Formamide
595. Carbon disulfide
596. Ethylene oxide
597. Bromoform
598. Isobutane
599. 2-Chloropropane
600. Isopropylamine
601. Dichloroethane 1,1-
602. Vinylidene chloride

603. 1,1-Difluoroethane
604. Vinylidene fluoride
605. Dichlorofluoromethane [FC-21]
606. Phosgene
607. Chlorodifluoromethane [FC-22]
608. Iodoform
609. Trimethylamine
610. Nitromethane
611. Propylene imine
612. Propylene oxide
613. Difluorodibromomethane
614. Trifluorobromomethane [F-13B1]
615. Butanol tert-
616. 1-Chloro-1, 1-Difluoroethane
617. Trichlorofluoromethane [FC-11]
618. Dichlorodifluoromethane [FC-12]
619. Chlorotrifluoromethane [FC-13]
620. Tetramethyl lead (as Pb)
621. Dimethylbutane 2,2-
622. Acetone Cyanohydrin
623. 2,2,2-Trifluoroethanol
624. Dichloropropionic acid 2,2-
625. 2,3,3,3,-Tetrafluoropropene
626. Titanium Tetrachloride
627. Iodine
628. Lithium hydride
629. Pentachloroethane
630. Trichloroacetic acid
631. Chloropicrin
632. Tetrachloro-2,2-difluoroethane [FC-112a] 1,1,1,2-
633. Tetrachloro-1,2-difluoroethane [FC-112] 1,1,2,2-
634. Trichloro-1,2,2-trifluoroethane [FC-113] 1,1,2-
635. Dichlorotetrafluoroethane [Cryofluorane]
636. Chloropentafluoroethane
637. Heptachlor
638. Perchloryl fluoride
639. Sodium bisulfite
640. Dichloro-2-butene 1,4-
641. Zinc chloride - Fume
642. Hydrogen chloride
643. Phosphoric acid
644. Hydrogen fluoride
645. Ammonia
646. Sulfuric acid
647. Isopropylaniline N-
648. Sodium metabisulfite
649. Nitric acid
650. Hexachlorocyclopentadiene
651. Dicyclopentadiene
652. Dimethyl sulfate
653. Nickel chloride (as Ni)
654. Phosphorus trichloride
655. Hydrogen peroxide
656. Tetrasodium pyrophosphate
657. Phosphorus (yellow)
658. Bromine
659. Barium sulfate
660. Chromic acid and Chromates (as CrO_3)
661. Lead chromate (as Cr)
662. Diesel fuel No. 4 - Vapor and aerosol
663. Ammonium sulfamate
664. Sodium persulfate (as S_2O_8)
665. Calcium sulfate
666. Arsenous acid, arsenic acid and salts (as As)
667. Fluorine
668. Graphite - All forms except graphite fibers
669. Selenium - Inorganic compounds (as Se)
670. Chlorine
671. Germanium tetrahydride
672. Hydrazoic acid
673. Hydrogen sulfide
674. Hydrogen selenide
675. Oxygen difluoride
676. Nitrogen trifluoride
677. Selenium hexafluoride
678. Tellurium hexafluoride
679. Lead arsenate (as As)
680. Mevinphos
681. Nickel sulfate (as Ni)
682. Strontium chromate (as Cr)
683. Bromine pentafluoride
684. Tetraethyl lead (as Pb)
685. Ethyl silicate
686. Triorthocresyl phosphate
687. Dioxathion - Vapor & Aerosol
688. Triethylphosphate
689. Isophorone
690. Isopentane
691. Isoprene
692. Isobutylamine
693. Isobutyronitrile
694. Isobutyl alcohol
695. Isobutyraldehyde
696. Propylene dichloride
697. Chloro-1-propanol 2-
698. Butanol sec-
699. Methyl ethyl ketone [MEK]
700. Phosphine
701. Antimony hydride [Stibine]
702. Silicon tetrahydride [Silane]
703. Trichloroethane 1,1,2-

704. Trichloroethylene
705. Chloroacetyl chloride
706. Acrylamide
707. Propionic acid
708. Acrylic acid
709. Monochloroacetic Acid
710. Methyl acetate
711. Nitroethane
712. Acetylene tetrabromide
713. Dimethylbutane 2,3-
714. Tetrachloroethane 1,1,2,2-
715. Chlorotrifluoroethylene
716. Methacrylic acid
717. Nitropropane 2-
718. Cumene Hydroperoxide
719. Oxybis(benzenesulfonyl hydrazide) p,p'-
720. Methyl methacrylate
721. Chlorinated camphene
722. Petroleum distillates [Naphtha]
723. Paraffin wax -Fume
724. Pyrethrum
725. Diphenyl ether / Biphenyl mixture (vapor)
726. Gasoline
727. Turpentine
728. Kerosene
729. Methyl demeton
730. Rubber solvent (Naphtha)
731. Asphalt (Bitumen) fume
732. Demeton - Vapor & aerosol
733. Warfarin
734. 1,1,1,2-Tetrafluoroethane
735. Pentachloronitrobenzene
736. Hexamethylene diisocyanate [HDI] 1,6
737. Pindone
738. Rotenone (commercial)
739. Diethyl phthalate
740. Dibutyl phthalate
741. Phthalic anhydride
742. Tributyltin naphthenate (as TBTO)
743. Azinphos-methyl - Vapor and Aerosol
744. ANTU
745. Trichlorobenzene 1,2,3-
746. Hexachlorobutadiene
747. Pentachlorophenol
748. 1-Decene
749. N-Methyl-2-Pyrrolidone
750. Nitrotoluene o-
751. Picric acid
752. Butylphenol o-sec-
753. Anisidine o -
754. Polyvinyl chloride [PVC]
755. Acrylic acid polymer
756. Cellulose
757. Starch
758. Naphthalene
759. Quinoline
760. Demeton-S-methyl - Vapor & aerosol
761. Biphenyl
762. Phenothiazine
763. Trichlorophenoxyacetic acid] 2,4,5-T [2,4,5-
764. Perlite
765. Benzoyl peroxide
766. Dichlorophenoxyacetic acid] 2,4-D [2,4-
767. Fonofos
768. Indene
769. Xylene o-
770. Cresol o-
771. Chlorotoluene o-
772. Dichlorobenzene o-
773. Toluidine o-
774. Phenylenediamine o-
775. Trimethyl benzene 1,2,4-
776. 2,4-Toluene Diamine and mixed isomers
777. Dibromo-3-chloropropane 1,2-
778. Methyl pentane 3-
779. Trichloropropane 1,2,3-
780. Diethyl ketone
781. Methyl Ethyl Ketoxime
782. Methyl acrylate
783. Methyl chloroacetate
784. Thiobis(6-tert-butyl-m-cresol) 4,4'-
785. Disulfiram
786. TetrahydrofurfurylAlcohol
787. Furfuryl alcohol
788. Furfural
789. Butyltoluene p-tert-
790. Butylphenol p-tert-
791. Butylbenzoic acid 4-tert-
792. Cumene
793. alpha-Methyl styrene
794. Acetophenone
795. Benzoyl Chloride
796. Nitrobenzene
797. Nitrotoluene m-
798. Dinitrobenzene m-
799. Hydroxybenzoic Acid
800. n,n-Dimethyl-para-toluidine
801. Nitrotoluene p-
802. tert-Amyl methyl ether [TAME]
803. Triethoxysilane
804. Hydroxypropyl acrylate 2-

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