The Tier 2 Occupational Exposure Banding Process: Using Information beyond GHS

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 (Table 3-1). Sources of toxicological information have been assessed and assigned as Rank 1 (preferred sources) or Rank 2 (second-level sources). Rank 1 sources are those that are most likely to contain 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. Additionally, Tier 2 has a data sufficiency threshold described fully later in section 3.2.

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

Toxicological Endpoint	
Cancer	Skin Sensitization
Reproductive and Developmental Toxicity	Acute Toxicity/Lethality (LD_{50} or LC_{50})
Systemic Target Organ Toxicity (STOT-RE)	Skin Irritation/Corrosion
Genotoxicity	Eye Irritation/Corrosion
Respiratory Sensitization	

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 NIOSH 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 endpoint determinant scores based on the presence of data for each health endpoint. The TDS is compared to a predetermined threshold for data sufficiency (see section 3.2). The 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 data is sufficient to assign a band. It informs the user whether or not there is adequate 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. It is important to note that the Tier 2 banding process relies on the data that is collected and recorded by the user and thus it is recommend that a user conduct a reassessment of the data every 6 months or as needed based up on the availability of new information/data.

3.1. Overall Strategy for Banding Chemicals in Tier 2

The overall Tier 2 process involves collecting quantitative and qualitative toxicity information on 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. Table 3-3 allows the user to quickly identify potential data sources for each endpoints. Data can be recorded electronically via the NIOSH Occupational Exposure Banding e-Tool or manually via the worksheets located in Appendix B of this document.

Endpoint-specific findings are documented in the worksheet, 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 e-Tool 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 broadly in Figure 3-1 and in detail in Figure 3-2.

Figure 3-1: Simple overview of Tier 2 process

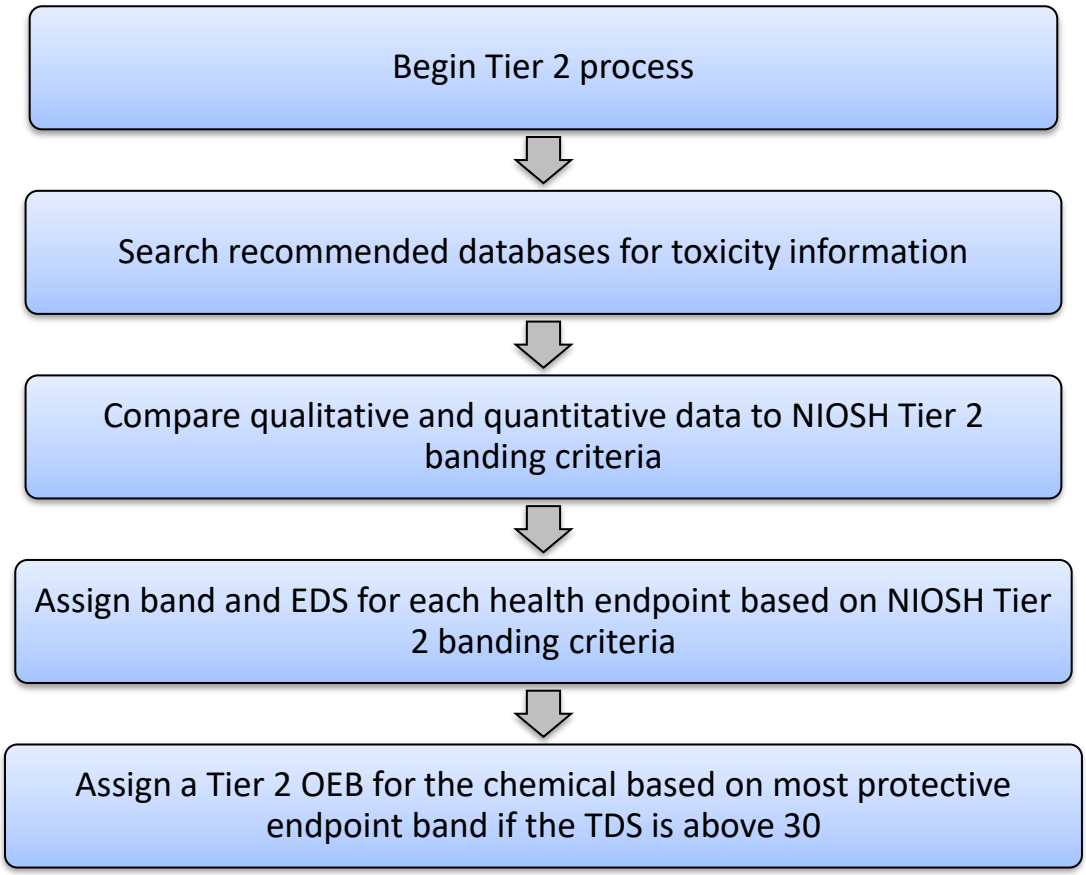

Figure 3-2: Detailed overview of Tier 2 process

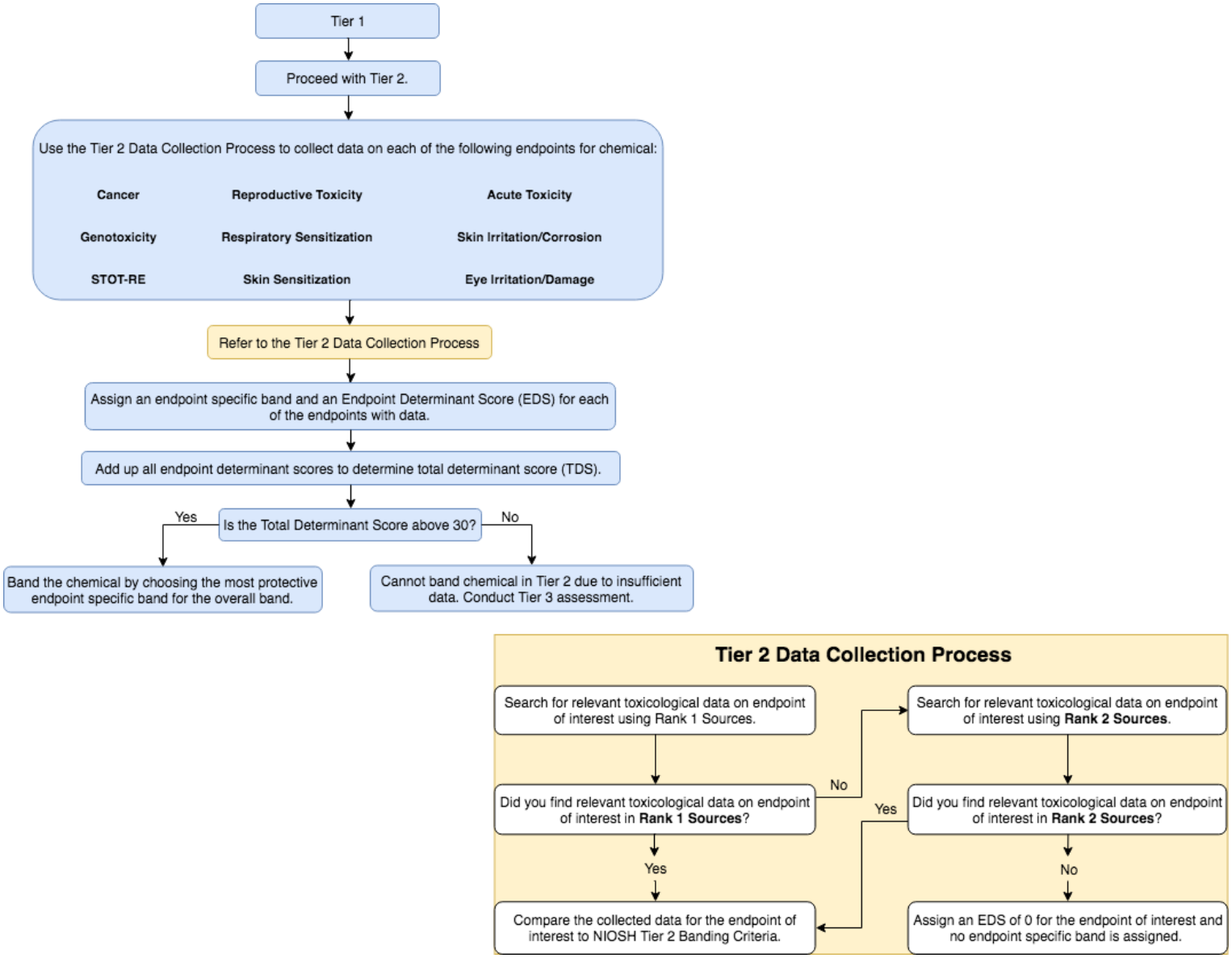

Table 3-2: List of Information Sources for Banding in Tier 2

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 [Health-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 [Health-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 [Health-Canada 1996]	HC
	2	European Chemicals Agency; Registration, Evaluation, Authorisation and Restriction of Chemicals [ECHA 2016]	REACH
		Organization for Economic Co-operation and Development [OECD 2016]	OECD
		World Health Organization International Programme on Chemical Safety [WHO-IPCS 2015]	WHO-IPCS
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

Skin Irritation/Skin Corrosion		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						

1

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. The TDS is the end product of a scoring system based on the availability of quantitative and/or categorical information on the entire range of toxicological outcomes.

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. 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 3-4, different scores are used for the presence of data on different toxicological outcomes. These EDS values represent weights for the relative importance and severity of the toxicological outcomes under consideration. Thus, the presence of cancer and the existence of quantitative data on systemic toxicological outcomes score higher than less severe or non-life-threatening outcomes, such as eye irritation. Recognizing this disparity, the scheme assigns to a chemical an EDS of 30 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 3-4, the data sufficiency threshold of 30 (out of a maximum possible TDS of 125)was selected empirically to ensure sufficient date from at least one of the more health-critical endpoints. 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 endpoints evaluated as the Tier 2 outcome. If this band 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 endpoint for banding where several data points may be available within a specific endpointcategory. 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 data points 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 are 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: Assigned Scores for the Presence of Toxicological Endpoints Encountered in the Tier 2 Evaluation

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

Table 3-5: Checklist for Tier 2 Hazard Banding

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

3.3. Banding Potentially Hazardous Chemicals on the Basis of Carcinogenicity

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

A *carcinogen* is 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 2015]

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

Data Sources – Carcinogenicity

Sources for Tier 2 information on carcinogenicity 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 band resulting from the quantitative assessment takes precedence.

Quantitative Assessment – Carcinogenicity

The quantitative assessment of carcinogenicity uses a measure of potency as a more accurate way to band chemicals than a purely qualitative-only approach. Because OEBs represent concentration ranges, potency information is more desirable in terms of selecting the appropriate band. Potency data, may be in the form of a slope factor (SF), an inhalation unit risk (IUR), or a tumorigenic dose (TD_{05}) or concentration (TC_{05}) associated with a 5% increase in tumor

incidence or mortality. To conduct a quantitative assessment, the potency measure is converted to appropriate units (if necessary) and compared to quantitative banding criteria to select the appropriate band 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 other sources listed in Table 3-5 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 an EDS of 30 points.

Qualitative Assessment – Carcinogenicity

In the qualitative assessment, sources in Table 3-2 should be checked for carcinogen classifications and assessed 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 an EDS of 30 and band E.
    - *Group C (possible human carcinogen* or *suggestive evidence of carcinogenic potential)*, assign an EDSof 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)*, an EDS 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 an EDS 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 an EDS of 30 and endpoint band E.
    - *Group 3 (not classifiable as to its carcinogenicity to humans)* or IARC has not classified the chemical, move to the next source. No EDS is assigned.
    - *Group 4 (probably not carcinogenic to humans),* assign an EDS of 30 and endpoint band A.

State of California Office of Environmental Health Hazard Assessment

- CalOEHHA 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 2015].

Data Sources – Reproductive Toxicity

Sources for Tier 2 information for reproductive toxicity can be found in Table 3-8. Standard 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 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 a 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 reviews of studies featuring oral, dermal, and inhalation exposures in experimental animals with an emphasis on 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 animals. If a NOAEL/BMDL or LOAEL is available, an EDS of 30 is assigned to indicate sufficient information is available for banding in Tier 2. The presence of multiple acceptable NOAEL/BMDL or LOAEL also warrants a score of 30. If there are no available data for reproductive toxicity, no band is assigned and an EDS of 0 is assigned. This score is based on the availability of the information, regardless of the outcome of the test or observation (positive/negative).

Unit Conversions for Inhalation Data – Reproductive Toxicity

The U.S. EPA [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 2015].

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) 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 and use, for each route, the single NOAEL/BMDL that is the most health-protective (most stringent). 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 preferred source of evidence for this endpoint and the associated bands. However since human data is not generally available, data from standard 28-day, 90-day or lifetime (up to 2 years) studies in rats and other experimental animals are more likely to provide information for this endpoint. More specifically, NOAELs/BMDLs identified in experimental animals following oral, dermal, and inhalation exposures are used to derive the endpoint specific band.

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 the 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 the chemical in Tier 2. The presence of multiple NOAEL/BMDL also warrants a score of 30. If there are no available data for STOT-RE, no band is assigned and an EDS 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).

3.6. 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 distinguish the two. 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 2015].

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 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 2015].

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 used to determine the overall band. Ultimatley, the most health-protective band (the most stringent)e based on the summary statements in authoritative reviews or evaluation of the data should be chosen. 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)

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 on genotoxicity are available, a score of 5 is assigned as the EDS. The presence of multiple acceptable studies also warrants a score of 5. If there are no available data for genotoxicity, no band is assigned and an EDS 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 2015]. 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 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 2015] has not proposed a specific quantitative potency criteria for Category 1 respiratory sensitizers.

NIOSH recommends banding criteria for respiratory sensitization on the basis of qualitative criteria, as set forth in Table 3-16. Due to the imprecision 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 respiratory sensitization can be drawn from conclusions provided in reviews from recommended databases listed in Table 3-15

Endpoint-Specific Band Selection – Respiratory Sensitization

The following steps are followed to assign a band:

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

Endpoint Determinant Score – Respiratory Sensitization

If acceptable data on respiratory sensitization are available, a score of 10 is assigned as the EDS. The presence of multiple acceptable studies also warrants a score of 10. If there are no available data for respiratory sensitization, no band is assigned and an EDS 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).

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

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

In Tier 2, skin sensitizers are assigned to one of five endpoint bands, ranging from band E (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 based on the GHS quantitative potency criteria for Category 1 (subcategories 1A and 1B) skin sensitizers. These criteria are based on human evidence, EC3 values in the mouse LLNA, and the percentage of positive animals in relation to the induction concentration tested in 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 2015]. Therefore, evidence from animal studies is often used and supplemented by observational data drawn from situations where humans have become exposed in either the workplace or 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 (most stringent) 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 three potency bands (A, C, or 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 tests, 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
Qualitative	Negative results	Mixed results	Positive results OR NIOSH SK-SEN notation

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 (most stringent) 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 endpoint and the associated bands, skin sensitization band selection can use data from standard animal studies in mice (LLNA) and guinea pigs (Buehler test and GPMT) 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 the guinea pig maximization test or 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 the guinea pig maximization test or Buehler test incidence data for sensitization.
3. If multiple LLNA EC3 values and/or incidence data for sensitization from the guinea pig maximization test or Buehler test are available, the most health-protective (most stringent) 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 –Skin Sensitization

If acceptable data on skin sensitization are available, a score of 5 is assigned as the EDS. The presence of multiple acceptable studies also warrants a score of 5. If there are no available data for skin sensitization, no band is assigned and an EDS 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).

3.9. 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. The most health-protective (most stringent) value by exposure route is used to determine the appropriate band according to the LD_{50}/LC_{50} technical criteria shown in Table 3-20. This determination is then entered into the Tier 2 checklist in the appropriate row and column.

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}) mg/kg bodyweight	>2,000	>300 to ≤ 2,000	>50 to ≤ 300	>5 to ≤ 50	≤ 5
Dermal toxicity (LD_{50}) mg/kg bodyweight	> 2,000	>1,000 to ≤ 2,000	>200 to ≤ 1,000	>50 to ≤ 200	≤ 50
Inhalation gases (LC_{50}) ppmV/4h	> 20,000	>2,500 to ≤ 20,000	>500 to ≤ 2,500	>100 to ≤ 500	≤ 100
Inhalation vapors (LC_{50}) mg/liter/4h	> 20.0	>10.0 to ≤ 20.0	>2.0 to ≤ 10.0	>0.5 to ≤ 2.0	≤ 0.5
Inhalation dusts and mists (LC_{50}) mg/liter/4h	> 5.0	>1.0 to ≤ 5.0	>0.5 to ≤ 1.0	>0.05 to ≤ 0.5	≤ 0.05

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

Acute toxicity data may be available from a variety 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 appropriate 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 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 does not provide 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:

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

Where: LC_{50} (t) = LC_{50} determined over t hours from the study being used; and t is the number of hours of exposure in the study being used to estimate the 4-hour equivalent value n = the ten Berge constant [ten Berge et al. 1986]. A default value of 1 is used for "n" when extrapolating from less than 4 hours to longer durations and a default value of 3 is used for "n" when extrapolating from more than 4 hours to shorter durations.

Table 3-21 gives (1) a list of adjustment factors, (2) the resulting 4-hour LC_{50} calculated from an experimentally derived value of 100 mg/m^3 for 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 Factor Example for Acute Toxicity*

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

**This examples uses a 4-hour LC50 calculated from an experimentally derived value of 100 mg/m3 for the different exposure periods*

As shown in Table 3-21, for exposures longer than 4 hours, the ten Berge derived 4-hour LC_{50} values are lower, and thus more health-protective (more stringent) than those calculated using Haber's rule. It is important to note 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.

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 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 acceptable data on acute toxicity are available, a score of 5 is assigned as the EDS. The presence of multiple acceptable studies also warrants a score of 5. If there are no available data for acute toxicity, no band is assigned and an EDS 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).

3.10. 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 2015].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 this health endpoint, in addition to supplemental information useful for hazard characterization purposes of such direct skin effects beyond irritation and corrosion, are available in 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 2015] 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 skin corrosion/irritation 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 (most stringent) band corresponding to those conclusions is selected. The assessment is based on the substance in pure form, unless banding is being developed for a specific product that includes diluted or 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 acceptable data on skin corrosion/irritation are available, a score of 5 is assigned as the EDS. The presence of multiple acceptable studies also warrants a score of 5. If there are no available data for skin corrosion/irritation, no band is assigned and an EDS 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).

3.11. 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 2015].

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 listed in Table 3-25
- When multiple classifications by various authoritative reviews exist, the most health-protective (most stringent) 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 eye irritant*.
(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 acceptable data on eye damage/irritation are available, a score of 5 is assigned as the EDS. The presence of multiple acceptable studies also warrants a score of 5. If there are no available data for eye damage/irritation, no band is assigned and an EDS 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).

3.12. Issues of Certainty Bounding Band Selection

The TDS as an (index, measure) of data sufficiency for banding, addresses a range of toxicological endpoints that are identified for a particular chemical but not the number of studies within each toxicological endpoint. 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 are 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, health effects 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 its 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 cohort 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 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 found in secondary sources such as HSDB, EHC documents, and in other secondary documents that 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 gave 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 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 differences in the OEB and OEL derivation process, the interpretation and use of the band and associated concentration range is similar to the 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 appropriate. 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 a banding strategy is that it does not attempt to force inappropriate precision from the hazard analysis. A categorical view of the bands also aligns with the practical consideration that exposure control strategies are also categorical in nature. In practice, combinations of controls available for a given exposure scenario are not infinite. The use of the bands as control ranges is consistent with common applications of the control-banding procedure. 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 for exposure control. The use of the lower end of the band is the most health-protective strategy if additional chemical-specific assessments are not being made to refine the OEB or the resulting default control strategies.

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.

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 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 NIOSH 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 using a Tier 3 assessment for fibers, 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]). Using the same rationale, NIOSH recommends that the occupational exposure banding process — when applied to nanoparticles — to be 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 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 health-protective (most stringent) band on the assumption that poorly soluble nanoscale agents will likely be an order of magnitude more toxic that their microscale equivalents.

  This recommendation 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 an association between increased total particle surface area and increased toxicity for poorly-soluble nanoscale particles. . 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 reliability. 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 health-protective (most stringent) 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.