THE NIOSH CHEMICAL CARCINOGEN POLICY:
CLASSIFYING CHEMICAL CARCINOGENS AND ESTABLISHING A TARGET RISK LEVEL

CHRISTINE WHITTAKER

PRESENTED AT THE JUNE 2019 HEALTH EFFECTS ADVISORY COMMITTEE, CAL/OSHA, OAKLAND, CALIFORNIA

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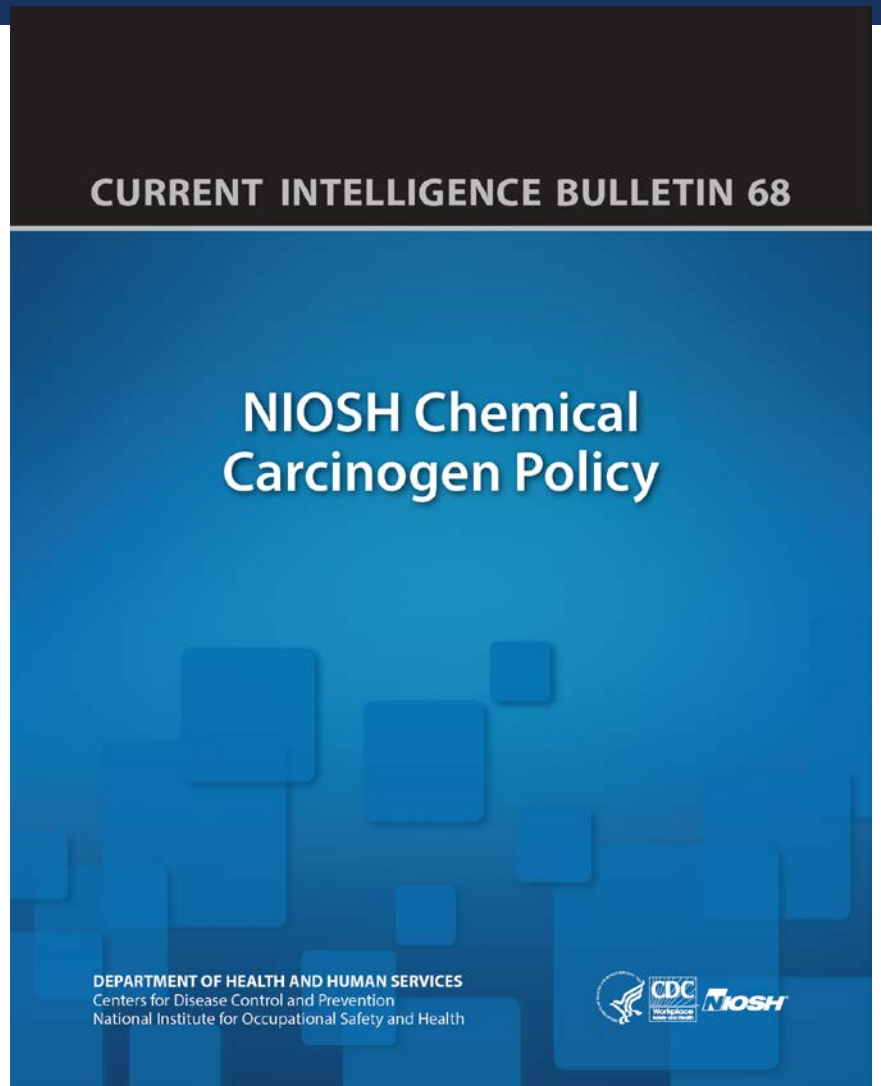


CANCER POLICY: THREE POLICIES

Carcinogen Classification

Carcinogen Risk Management Limit

Analytical feasibility

CARCINOGEN CLASSIFICATION: AUTHORITATIVE CLASSIFICATIONS

NTP	EPA	IARC
• Known to be a human carcinogen • Reasonably anticipated to be a human carcinogen	• Group A, Group B1, Group B2, Group C • Carcinogenic to humans, Likely to be carcinogenic to humans, Suggestive evidence of carcinogenic potential	• Group 1, Group 2A, Group 2B

WHY DIDN'T NIOSH CONSTRUCT A CLASSIFICATION SCHEME?

- Many existing schemes to choose from (and all are similar in strategy)
- Risk management strategies do not change based on degree of certainty in classification
- In the event that NIOSH classifies a carcinogen, the Globally Harmonised System (GHS) scheme is appropriate

CLASSIFICATION: RETROSPECTIVE OR PROSPECTIVE?

- Initially, planned a retrospective adjustment of the chemical classifications in the *NIOSH Pocket Guide to Chemical Hazards*
- This has proven not immediately feasible
- Existing classifications remain [Ca] and the list of NIOSH carcinogens is not entirely consistent with EPA, IARC or NTP.

CARCINOGEN CLASSIFICATION: OCCUPATIONAL RELEVANCE

Industrial usage

- Worker exposures
- Current production/import/use

Science review

- Is evidence current?
- Do new sources of information cast doubt on classification?

IF NO AUTHORITATIVE CLASSIFICATION

NTP Review

- NIOSH can nominate to NTP for review of evidence

NIOSH Review

- If NTP declines, or chemical is of particular interest to NIOSH, NIOSH can review
- Criteria to be used are GHS Cancer Classification Criteria

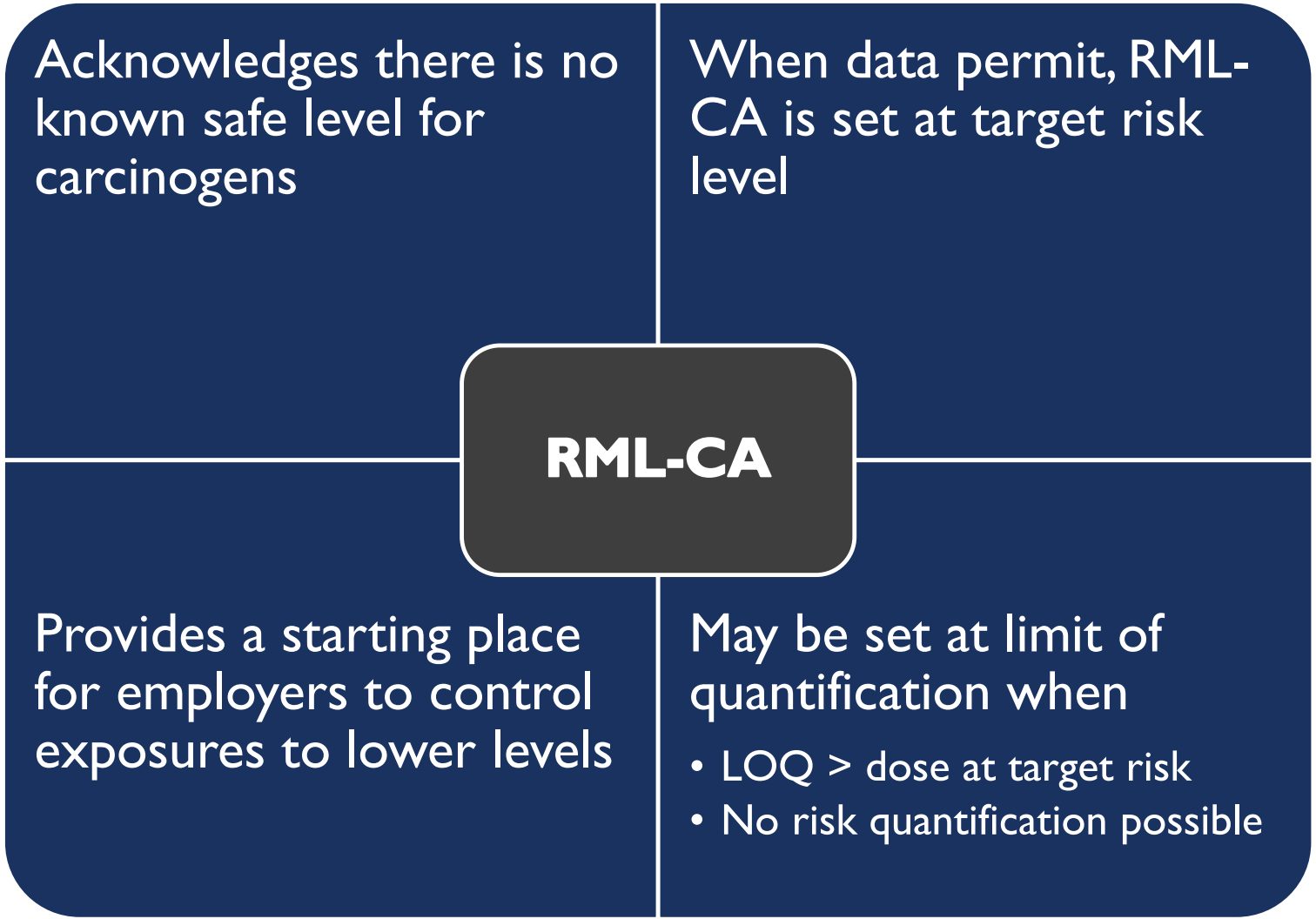
TERMINOLOGY

Why? Concern that known human carcinogens, such as asbestos, benzene and cadmium, shouldn't be characterized as "potential."

RISK MANAGEMENT LIMIT FOR CARCINOGENS

- No more RELs for Carcinogens!

RISK MANAGEMENT LIMITS FOR CARCINOGENS (RML-CA)



FUTURE CLASSIFICATIONS

- Currently, as we review individual chemicals, classifications are made consistent with the *Carcinogen Policy*.
- Result: the *Pocket Guide* will go through an awkward stage where policies from different time periods apply to different chemicals.
- Example: one chemical may have no numerical REL, but a Ca designation. Another chemical may be a NIOSH *occupational carcinogen* with a numerical RML-Ca.

ANALYTICAL FEASIBILITY AND ENGINEERING ACHIEVABILITY

Analytical Feasibility

- If higher than risk estimate at 1/10,000, LOQ will drive the RML-CA
- If used for RML-CA, risk estimated at LOQ

Engineering Achievability

- No longer considered in setting exposure limits
- Information on controlling exposures will continue to be provided

TARGET RISK LEVEL

Quantitative exposure-response data are gathered

Statistical modeling of exposure-response data

Central tendency and lower confidence limit for a range of risks are estimated (1/100-1/1,000,000)

RML-CA is set at the lower confidence limit on the 1/10,000 risk (10X lower than previous practice) **(unless it is lower than LOQ)**

TARGET RISK LEVEL

- Target risk level needed to set RML-CA. Target risk level is defined as the lower 95% confidence limit on the concentration corresponding to a risk estimate of 1 excess cancer per 10,000 workers exposed for a 45-year working lifetime.

APPROACHING THE PROBLEM

- NIOSH sought:
  - Input of peer reviewers
  - Stakeholders' comments
  - Other regulatory and recommending organizations' comments
  - Discussions with bioethicists

ISSUES IN DERIVING A TARGET RISK LEVEL FOR CANCER

- Revising the Carcinogen Policy gave us a chance to rethink target risk
  - Is cancer risk different from other chronic health endpoints?
  - Are occupational exposures "different" from environmental exposures?
  - What language is used to describe the risk level?
  - What level is the "right" level?
  - What evidence supports target risk level?

IS CANCER RISK DIFFERENT FROM OTHER CHRONIC HEALTH ENDPOINTS?

- Cancer as a health endpoint
  - Seriousness
  - Irreversibility
  - Dread
- Other health endpoints?
  - Lung disease (pneumoconiosis, COPD)
  - Neurological endpoints
  - Reproductive and/or developmental hazards
  - Chronic target organ toxicity (liver, kidney damage)

ARE OCCUPATIONAL EXPOSURES "DIFFERENT" FROM ENVIRONMENTAL EXPOSURES?

- Environmental organizations have considered environmental risks from 1/10,000 to 1/1,000,000 to support environmental regulations
  - Should risks to workers be higher?
  - Should the benefits conferred from working be considered in setting a target risk?

WHAT LANGUAGE IS USED TO DESCRIBE THE RISK LEVEL?

LANGUAGE

- More complex than it seems. Fraught with “loaded language”.
- Acceptable risk, minimal risk, negligible risk, target risk, maximum tolerated risk, just about tolerable risk . . .

LANGUAGE CAN BE LOADED

- Why "acceptable risk" is not always an "acceptable" term
- Importance of risk communication
  - Comparison of risks – advantages and pitfalls
  - Ignoring the denominator issue

WHAT LEVEL IS THE "RIGHT" TARGET LEVEL OF RISK?

- Considerations in setting target level of risk
  - Whether it is explicit or not, there is always a risk/benefit
  - Under-protection leaves too many at risk
  - Over-protection may force substitution into riskier solutions, other hazards
  - Striving for "reasonableness" – but who determines what is reasonable?

WHAT EVIDENCE SUPPORTS TARGET RISK LEVEL?

- Scientific evidence versus policy determination
  - Societal decisions – whose values are represented?
  - The ever-present "reasonable" human
  - Factors of 10
  - Precedents

NIOSH HISTORY OF TARGET RISK

- 1970s: No acceptable exposures to carcinogens (the Delaney Clause)
- 1980: U.S. Supreme Court "Benzene Decision" characterized a range of acceptable risks between 1 in 1000 and 1 in a billion
  - Stated that 1 in 1000 could be considered a significant risk
    - How OSHA has interpreted 1 in 1000 (residual significant risk)
    - How NIOSH has interpreted 1 in 1000 (consistency with OSHA)

HISTORY OF USE OF 1 IN 1000 RISK LEVEL

- 1990 Benzene PEL (journal article, testimony to OSHA)
- 1990 Cadmium PEL (testimony to OSHA)
- 1991 1,3-Butadiene PEL (testimony to OSHA)
- 1995 Coal dust (REL) – NON-cancer
- 1998 Diesel exhaust (journal article)
- 2001 Silica (journal article)

HISTORY – CONT.

- 2007 Manganese (journal article) – NON-cancer
- 2011 Titanium dioxide (RELs)
- 2012 Carbon nanotubes and nanofibers (REL) – NON-cancer
- 2013 Hexavalent chromium (REL)
- 2016 Diacetyl/2,3-Pentanedione (RELs) – NON-cancer

PRECEDENTS

- Surveyed other organizations that set target risk levels
- Compared (when possible) to previous NIOSH position, noting rationale

HEALTH COUNCIL OF THE NETHERLANDS

Table 1 Risk levels used for limiting exposure to carcinogenic compounds in the workplace and in the environment.

		Risk period	Exposure period [a]	Risk level
Occupational Health and Safety	Prohibitive risk	Life	Working life	4×10^{-3}
			One year	1×10^{-4}
	Target risk	Life	Working life	4×10^{-5}
			One year	1×10^{-6}
Environment	Maximum tolerable risk	Life	Lifetime	1×10^{-4}
			One year	1×10^{-6}
	Negligible risk	Life	Lifetime	1×10^{-6}
			One year	1×10^{-8}

[a] For the calculation of the risk related to the exposure during a full (working) lifetime, a period of 40 years for workplace exposure and a period of 100 years for environmental exposure is taken into account.

HEALTH AND SAFETY EXECUTIVE OF THE UK

Acceptable risk (annual)

- **1 in 1000 per year as the 'just about tolerable risk' for any substantial category of workers for any large part of a working life.**
- 1 in 10,000 as the 'maximum tolerable risk' for members of the public from any single non-nuclear plant.
- 1 in 100,000 as the 'maximum tolerable risk' for members of the public from any new nuclear power station.
- 1 in 1,000,000 as the level of 'acceptable risk' at which no further improvements in safety need to be made.

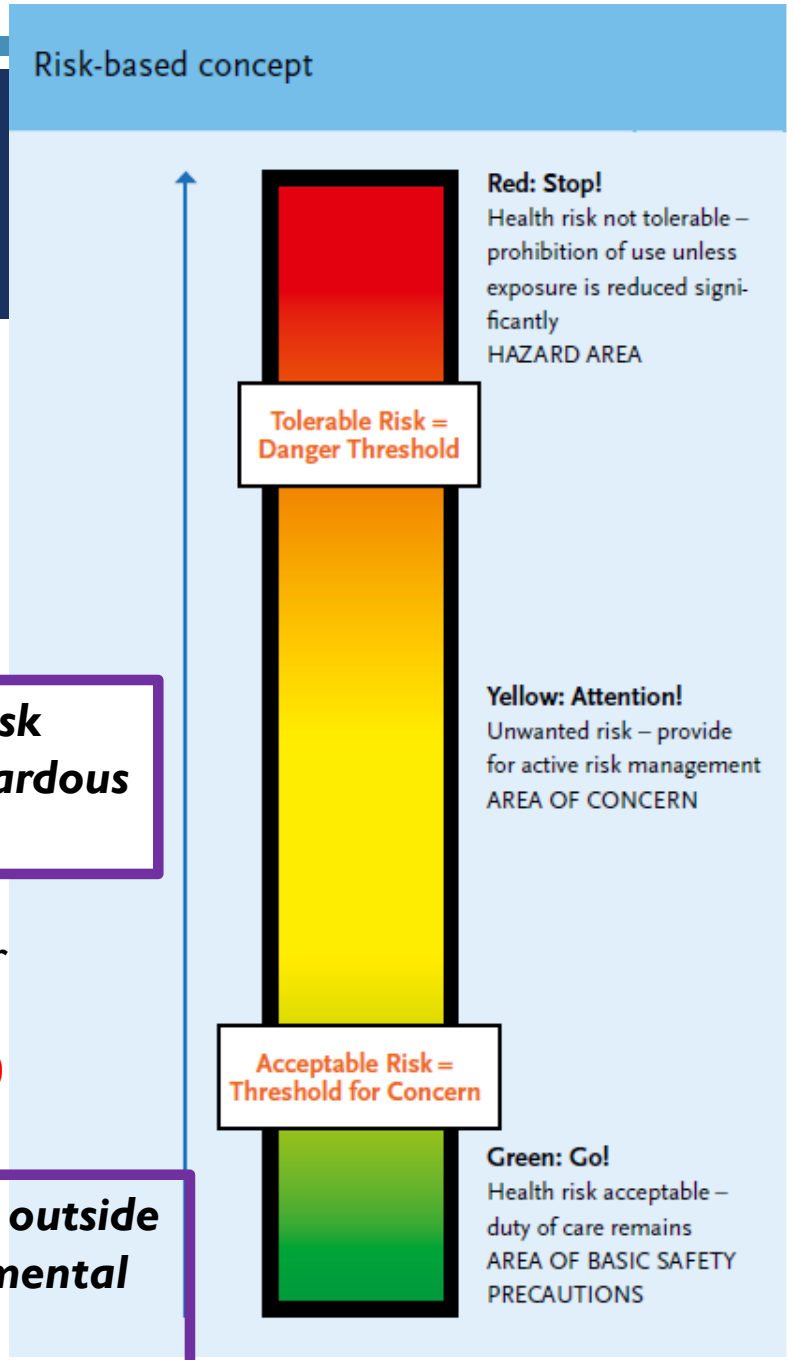
GERMANY

The **tolerable risk** defines the additional cancer risk of **4:1,000** that is tolerated, meaning that, statistically, 4 out of 1,000 persons exposed to the substance throughout their working life will develop cancer.

This value corresponds to the lung cancer risk of a non-smoker who is not exposed to hazardous substances at work.

The **acceptable risk** defines the additional cancer risk of **4:10,000** that is accepted during an initial phase . . . this will be reduced to **4 out of 100,000 cases.**

This value corresponds to the risk of cancer outside the workplace ("remaining general environmental risk").



SWEDEN

- Acceptable risk for genotoxic carcinogens of 1/100,000

US ARMY

- Acceptable risk = 1/10,000 (annual)
- "Career" deployments ~ 10 yrs = 1/1000 "working lifetime" risk.

SUMMARY

Relies on NTP, EPA and IARC for carcinogen classification

Sets new terminology (occupational carcinogen and RML-CA)

Changes our long-held policy on target risk to 1/10,000

When the LOQ > 1/10,000 risk level, LOQ = RML-CA

Questions?

NIOSH OCCUPATIONAL EXPOSURE BANDING PROCESS

THE FINDINGS AND CONCLUSIONS IN THIS PRESENTATION HAVE NOT BEEN FORMALLY DISSEMINATED BY THE NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH AND SHOULD NOT BE CONSTRUED TO REPRESENT ANY AGENCY DETERMINATION OR POLICY.

NIOSH OEB TEAM MEMBERS

- Stephen J. Gilbert, M.S.
- Thomas J. Lentz, Ph.D.,
- Lauralynn Taylor McKernan, Sc.D., CIH,
- Pranav Rane, M.P.H
- Melissa Seaton, M.S.,
- Christine Whittaker, Ph.D.

DOCUMENT OBJECTIVE

To create a consistent and documented process to characterize chemical hazards so timely and well-informed risk management decisions can be made for chemicals lacking OELs.

IMPORTANT POINT

An OEB is not meant to replace an OEL, rather it serves as a starting point to inform risk management decisions.

WHAT IS OCCUPATIONAL EXPOSURE BANDING?

A mechanism to quickly and accurately assign chemicals into "categories" or "bands" based on their health outcomes and potency considerations

Higher Concentrations

Lower Concentrations

PROPOSED NIOSH OCCUPATIONAL EXPOSURE BANDS

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

IS THIS THE SAME AS CONTROL BANDING? NO.

- ***COSHH Essentials*** is a control banding tool that helps small and medium-sized enterprises to do risk assessments for chemicals and mixtures of chemicals
  - identifies the control band (control approach),
  - produces advice on controlling risk from the chemical used in the specified task, and
  - provides written guidance and documentation as a result of the assessment
  - NIOSH has reviewed control banding strategies previously
- NIOSH Occupational Exposure Banding is NOT Control Banding

HOW IS THE PROCESS ORGANIZED?

Bands are assigned based on the findings for nine standard toxicological endpoints:

- acute toxicity
- skin corrosion and irritation
- serious eye damage and irritation
- respiratory sensitization
- skin sensitization
- genotoxicity
- carcinogenicity
- reproductive/developmental toxicity
- specific target organ toxicity resulting from repeated exposure

Tier 1 —GHS Hazard Codes

User: Health and safety generalist

A Tier 1 evaluation utilizes GHS Hazard Statements and Categories to identify chemicals that have the potential to cause irreversible health effects.

Tier 2— Secondary Data Sources

User: Properly trained occupational hygienist

A Tier 2 evaluation produces a more refined OEB, based on point of departure data from reliable sources. Data availability and quality are considered.

Tier 3—Expert Judgement

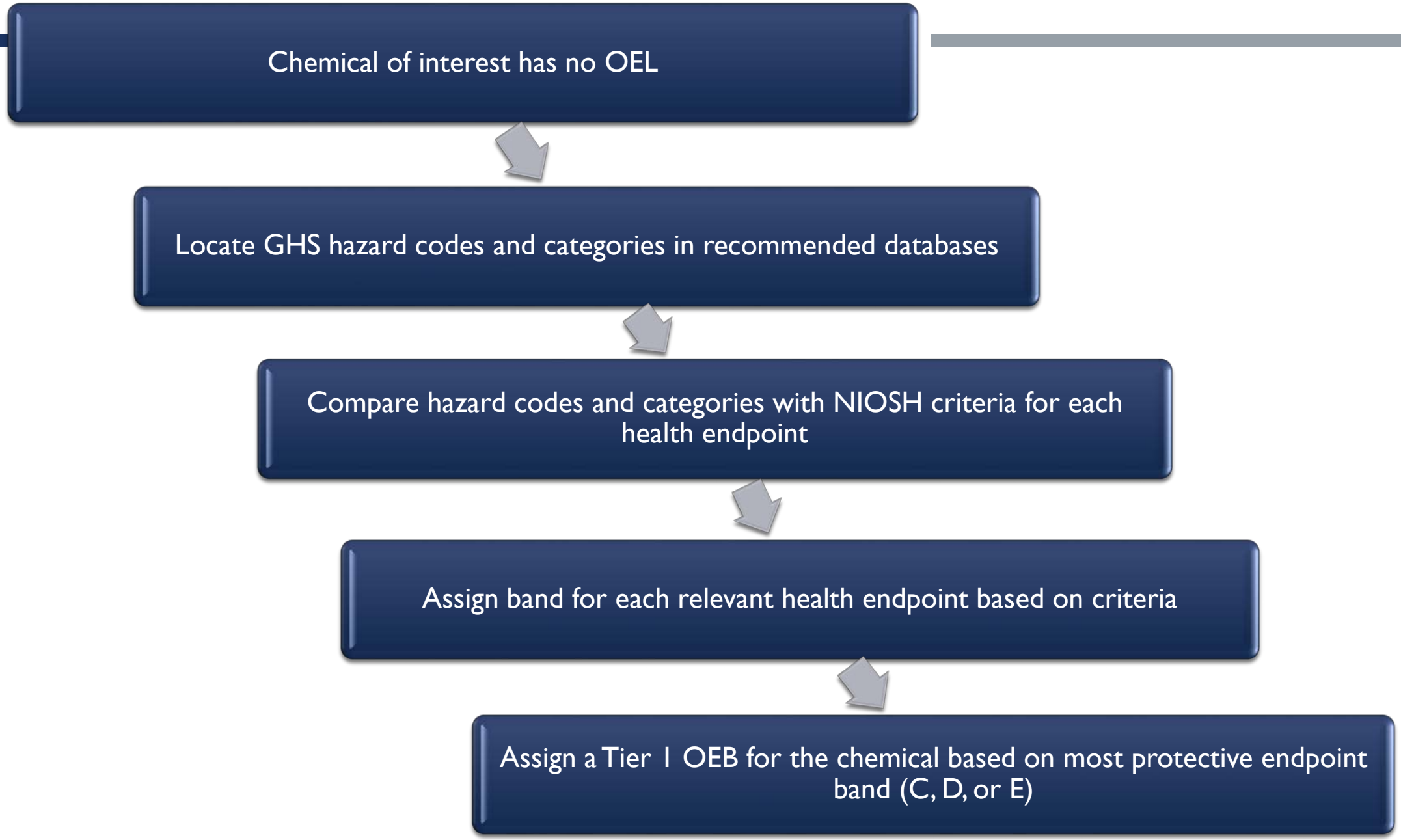
User: Toxicologist or experienced occupational hygienist

Tier 3 involves the integration of all available data and determining the degree of conviction of the outcome.

GLOBALLY HARMONIZED SYSTEM OF CLASSIFICATION AND LABELING OF CHEMICALS

- GHS is a hazard classification system developed by the United Nations to standardize chemical regulations in different countries
  - Within GHS, each physical or health hazard is a **hazard class** (e.g., Carcinogenicity is a hazard class)
  - A hazard class may be sub-divided into several **hazard categories** based on the severity of the hazard
  - GHS uses alphanumeric **hazard codes** to represent these hazards

TIER 1 OVERVIEW



TIER 1 Criteria		C	D	E
OEL Ranges	Particle	> 0.1 to ≤ 1 milligrams per cubic meter of air (mg/m^3)	> 0.01 to ≤ 0.1 mg/m^3	≤ 0.01 mg/m^3
	Vapor	> 1 to ≤ 10 parts per million (ppm)	> 0.1 to ≤ 1 ppm	≤ 0.1 ppm
Acute Toxicity		H301 Category 3	H300 Category 2	H300 Category 1
		H302 Category 4		
		H331 Category 3	H330 Category 2	H330 Category 1
		H332 Category 4		
		H311 Category 3	H310 Category 2	H310 Category 1
		H312 Category 4		
Skin Corrosion/ Irritation		H315 Category 2		H314 Category 1, 1A, 1B, or 1C
Serious Eye Damage/ Eye irritation		H319 Category 2, 2A or 2B		H318 Category 1
Respiratory and Skin Sensitization		H317 Category 1B	H317 Category 1 or 1A	
			H334 Category 1B	H334 Category 1 or 1A
Genotoxicity			H341 Category 2	H340 Category 1, 1A or 1B
Carcinogenicity				H350 Category 1, 1A, or 1B
				H351 Category 2
Toxic to Reproduction		H361 (including H361f, H361d, and H361fd) Category 2	H360 (including H360f, H360d, and H360fd) Category 1B	H360 (including H360f, H360d, and H360fd) Category 1 or 1A
Specific Target Organ Toxicity		H371 Category 2		H370 Category 1
		H373 Category 2		H372 Category 1

RELIABLE SOURCES FOR TIER 1

- GESTIS SubstanceDatabase

  www.dguv.de/ifa/gestis-database

- ECHA Annex VI to CLP

TIER 2

Tier 2 is always recommended, but especially useful when:

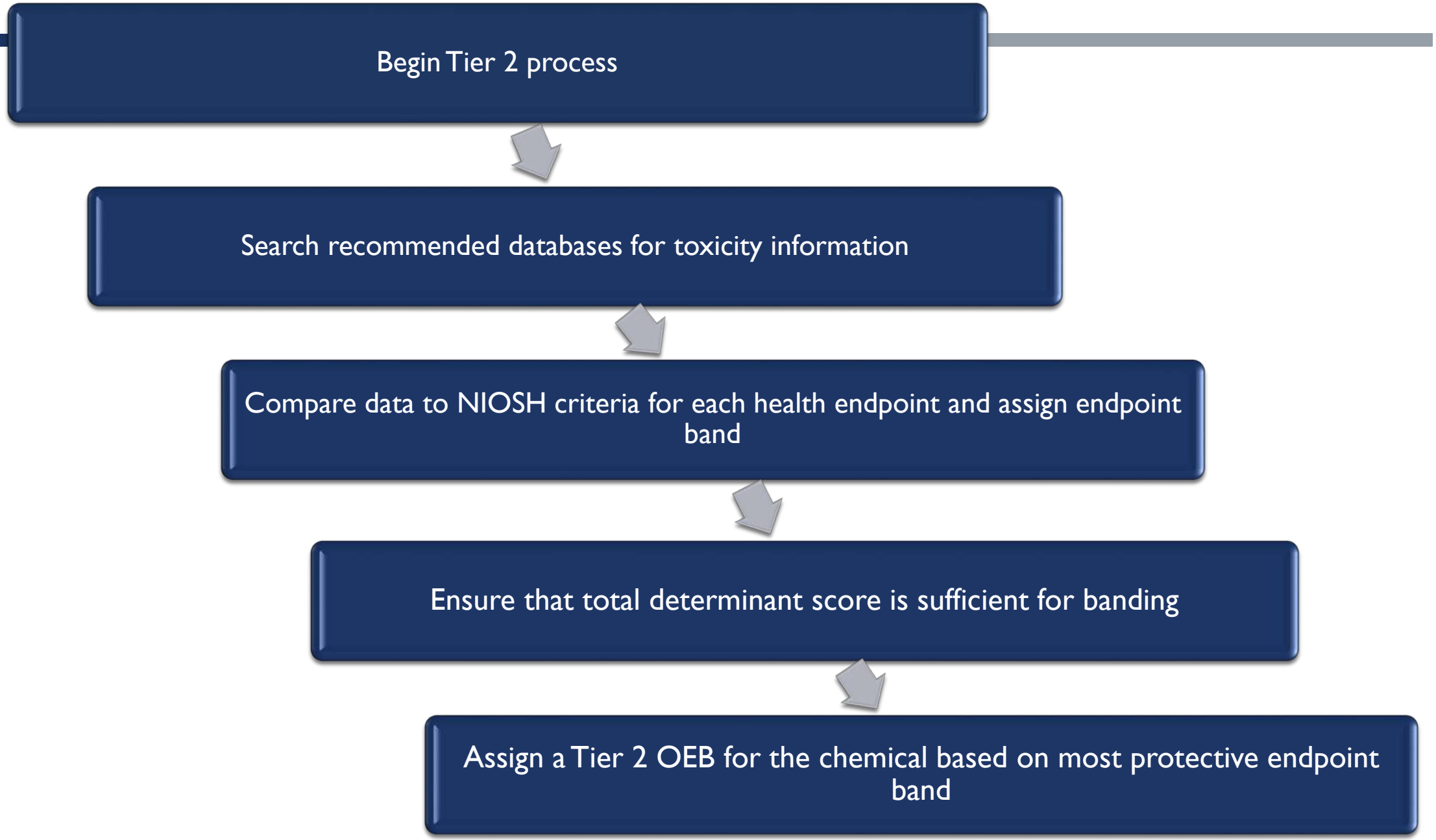
- there are no GHS H codes
- the outcome of the Tier 1 analysis is incomplete, or an insufficient reflection of the health potency of the chemical

TIER 2

Tier 2 — Both Qualitative and Quantitative

- Some training in toxicology
- Based on readily available secondary data from authoritative sources (government, professional health agencies, authoritative toxicological benchmarks)
- Needs sufficient data to generate reliable OEB
- Prescriptive analytical strategy to ensure consistency
- Potential for chemicals to be moved from the Tier 1 OEB to a more or less protective OEB

TIER 2 OVERVIEW



TIER 2 BANDING PROCESS

- ***Search authoritative databases for summary toxicity information:***

  For 9 specified health endpoints, search authoritative databases for summary toxicity information

- ***Combine information through a weighted score:***

  Find the weighted score (Total Determinant Score) and calculate the Occupational Exposure Band (this is done automatically in the e-Tool)

TOTAL DETERMINANT SCORE

- **Endpoint determinant score (EDS) =** weighted score indicating the presence/absence of data for a specific health endpoint.
- **Total determinant score (TDS) =** sum of weighted scores for each health endpoint. Overall score gives an indication of sufficiency of data for banding. **TDS ≥ 30: sufficient data for banding in Tier 2**

Example: a cancer inhalation unit risk value tells us a lot about the hazardous nature of a chemical, so the presence of that information corresponds to a TDS of 30. However, an LD_{50} value for the acute toxicity endpoint is only weighted as a TDS of 5.

TOTAL DETERMINANT SCORE

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

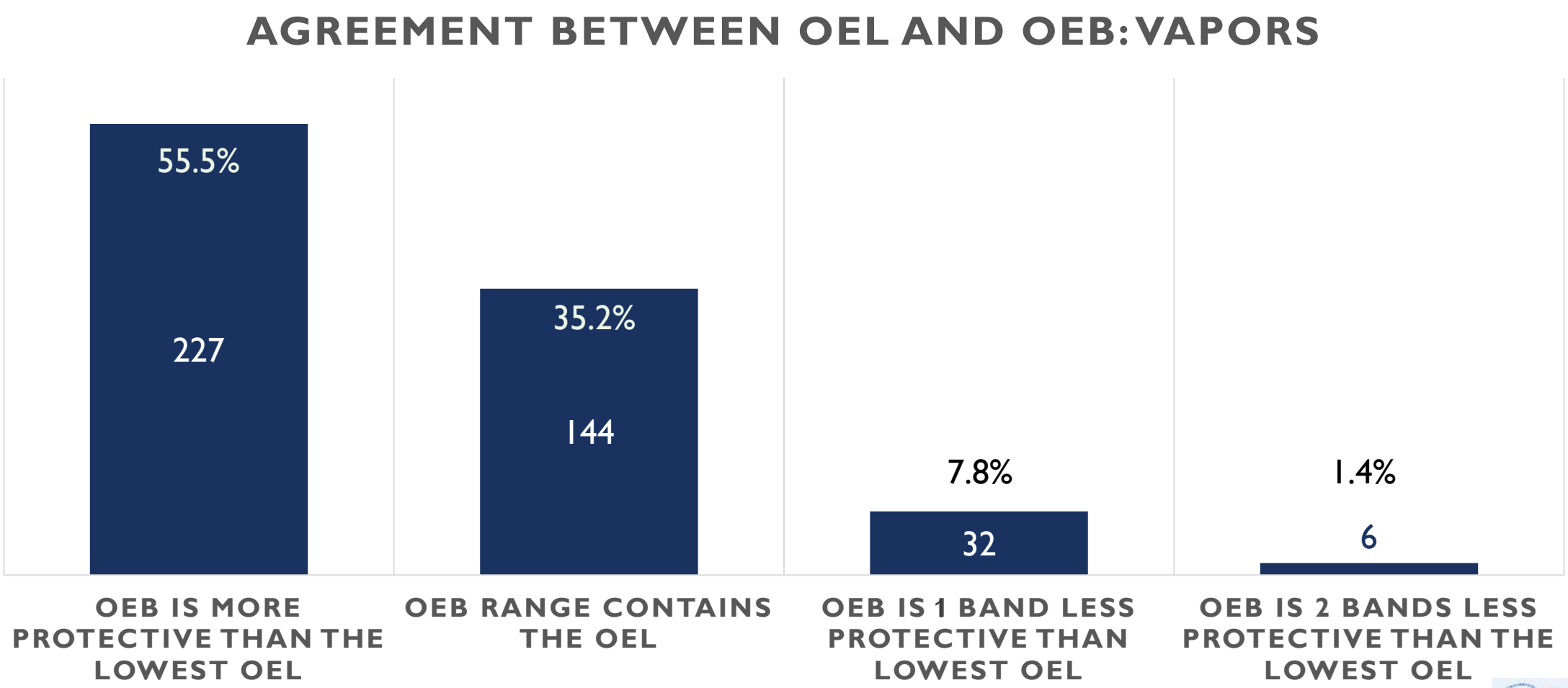
Recommendation --- Rane Test 1(1)

Chemical Name: Rane Test 1 CAS Number: 1				
Liquid/Vapor Range: <= 0.1 ppm **Particle Range:** <= 0.01 mg/m³				
Recommended Band			**TDS=85**	**E**
Endpoint	**Source**	**Data**	**EDS**	**Endpoint Band**
Carcinogenicity Quant	EPA IRIS Slope Factor	1 x 0.00001 (mg/kg-day)⁻¹	30	C
	California Slope Factor	1 x 0.000001 (mg/kg-day)⁻¹		C
Carcinogenicity WOE	U.S. EPA IRIS	Group C (possible human carcinogen)	20	D
Reproductive Toxicity				
Target-Organ Toxicity	U.S. EPA: IRIS	Rank: 1; NOAEL; 90 hrs; 4.8 ppm	30	E
Genotoxicity Toxicity				
Respiratory Sensitization	WHO: International Programme on Chemical Safety	Rank: 1; Results: Mixed	10	C
Skin Sensitization				
Acute Toxicity	National Library of Medicine ChemID Plus	Rank: 1; Type: Oral LD50; Duration: 4.00 hrs; Input: 661	5	B
Skin Irritation	WHO: International Programme on Chemical Safety	Rank: 1; Results: Skin corrosion/irreversible effects	5	E
	Organization for Economic Co-operation and Development	Rank: 1; Results: Moderate to severe irritation		C
Eye Irritation	WHO: International Programme on Chemical Safety	Rank: 1; Results: Irreversible eye damage	5	E
Notes	**Carcinogenicity:** Cancer Test Information: https://ntp.niehs.nih.gov/pubhealth/roc/index.html			
	STOT: STOT Test Information: https://ntp.niehs.nih.gov/testing/types/heathandsafety/index.html			
	Acute Tox: Acute Toxicity Information: http://www.inchem.org/			

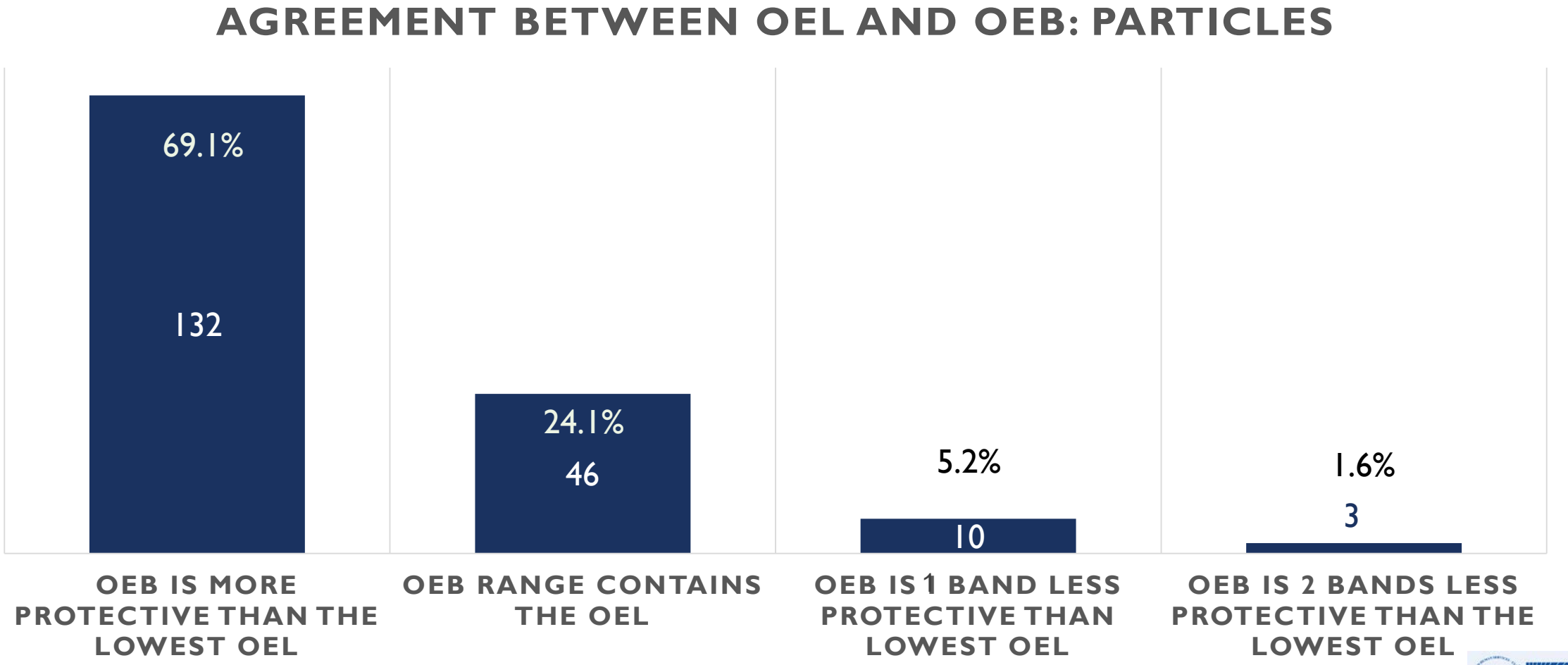
TIER 3 BANDING PROCESS

- Requires expert in toxicology
- Requires intensive review and evaluation of primary data
- Is required when insufficient data for Tier 2 banding
- No detailed guidance is available

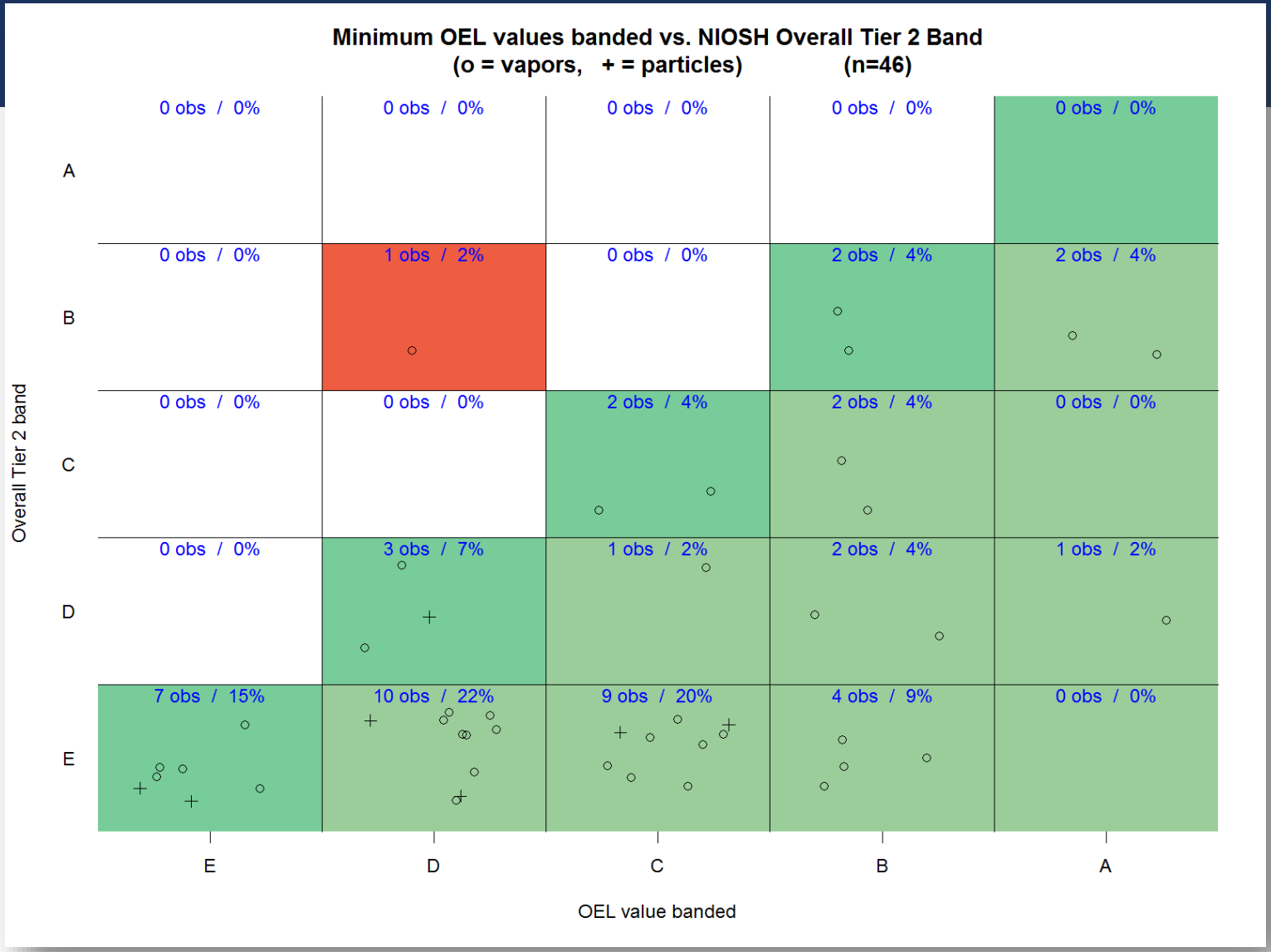
TIER 1 EVALUATION:VAPORS



TIER 1 EVALUATION: PARTICLES



TIER 2 EVALUATION



NIOSH OCCUPATIONAL EXPOSURE BANDING TOPIC PAGE

- https://www.cdc.gov/niosh/topics/oeb/default.html

CASE STUDY: BISPHENOL A

Table 2. Tier 1: Occupational exposure banding results for BPA under Draft NIOSH Occupational Exposure Banding Process.

Endpoint	Hazard Code*	Hazard Category	Hazard Statement	Endpoint Band
Acute Toxicity	None			
Skin Corrosion/Irritation	None			
Eye Damage/Irritation	H318	1	Causes serious eye damage	E
Respiratory and Skin Sensitization	H317	1	May cause an allergic skin reaction	D
Germ Cell Mutagenicity	None			
Carcinogenicity	None			
Reproductive Toxicity	H360F	1B	Suspected of damaging fertility	D
Specific Target Organ Toxicity – Repeated Exposure	None			

BISPHENOL A TIER 2 RESULTS

Endpoint	Health Effect	Number of data points/ study info	Endpoint Band	Endpoint Determinant Score
Acute toxicity	LD_{50}	10; guinea pig, mouse, rabbit, rat; oral	**A**	5/5
Skin corrosion/ irritation	Descriptor	2; dermal	**A**	5/5
Eye damage/ irritation	Descriptor	1	**E**	5/5
Respiratory sensitization	No data			0/5
Skin sensitization	LLNA Descriptor	2 1 (case report)	**A (E)**	5/5
Genotoxicity	Descriptor	3	**A**	5/5
Carcinogenicity	No data			0/30
Reproductive toxicity	NOAEL	21 Rat, mouse; oral; multigen	**C or E (A-E)** Depending on studies included in analysis	**30/30**
Specific target organ	NOAEL	3 Mouse, rat; oral, inhalation	**D (B-D)**	**3030**

THANK YOU!