Case Study Summary

Title: Occupational Exposure Banding 2.0: Characterizing Risks for Chemicals with Limited Data

Version:

Presented by:

Panel Advisor:

1. Provide a few sentences summarizing the method illustrated by the case study.

Summary

NIOSH has developed an occupational exposure banding tool that relies on a defined minimum array of available data to generate an occupational exposure band. While the NIOSH occupational banding tool is useful for chemicals with some data, but no authoritative occupational exposure limits, NIOSH is exploring potential methods to augment the banding tool to assess chemicals with insufficient data to band them with the current tool. The methods under investigation to augment the banding tool include read across and QSAR methods. In this preliminary case study, NIOSH is soliciting peer input regarding the advantages and disadvantages of various approaches that could be standardized for assessing the potential hazards of chemicals with limited data. NIOSH is also soliciting input on how best to use such techniques, whether as a method to refine Tier 1 or Tier 2 banding results to fill in gaps, or to only use such techniques when there is insufficient data to establish an occupational exposure band.

Background

Occupational exposure limits (OELs) play a critical role in protecting workers and emergency response personnel from exposure to dangerous concentrations of hazardous materials. In the absence of an OEL, determining the appropriate controls needed to protect workers from chemical exposures can be challenging. Of the more than 85,000 chemicals that are commercially available, only about 1,000 of these have been assigned an authoritative (government, consensus, or peer reviewed) OEL. Furthermore, the rate at which new chemical substances are being introduced into commerce significantly outpaces OEL development, creating a need for guidance on thousands of chemical substances that lack reliable exposure limits. One of the challenges faced by occupational hygienists and safety professionals is that despite the myriad sources of data on chemical substances, a uniform decision-making framework is not currently available to screen and discriminate the most relevant data when assessing chemical substances and developing exposure control guidance. Occupational exposure banding is a systematic process in which users identify qualitative and quantitative hazard information on selected health-effect endpoints and compare those data to NIOSH banding criteria to identify potential exposure ranges.

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The unique attributes of the NIOSH process include: (1) a three-tiered system that allows users of varying expertise to use the process; (2) determination of potential health impacts based on nine health endpoints; (3) hazard-based categories linked to quantitative exposure ranges; and (4) NIOSH evaluation of the process to determine consistency of the occupational exposure banding process with OELs.

The banding protocol is divided into three tiers. Most users would employ Tier 1 and Tier 2. Specialized expertise is needed to implement Tier 3. A primary goal of Tier 1 is to give the user a quick summary of the most important health effects associated with exposure to the chemical substance of interest and to quickly identify toxic chemical substances that should be considered for substitution or elimination. Tier 1 is based solely on the Globally Harmonised System of Classification and Labelling (GHS) and is automated in the NIOSH e-Tool at https://wwwn.cdc.gov/Niosh-oeb/ .

Tier 2 requires the user to examine a number of publicly available databases and extract relevant toxicological and weight-of-evidence data to be used in the NIOSH banding algorithm. NIOSH has a higher confidence in occupational exposure bands based on the Tier 2 protocol, as compared to Tier 1. However, Tier 2 requires a significant amount of user effort and some facility with toxicological data. Tier 3 employs a critical assessment of all relevant information to evaluate experimental data and discern toxicological outcomes and is usually undertaken only by expert toxicologists or risk assessors.

Nine toxicological health endpoints are considered in the banding protocol: (1) carcinogenicity; (2) reproductive toxicity; (3) specific target organ toxicity; (4) genotoxicity; (5) respiratory sensitization; (6) skin sensitization; (7) acute toxicity; (8) skin corrosion and irritation; and (9) eye damage/irritation.

Once the chemical toxicity data is gathered and compared to the NIOSH criteria, the chemical substance is assigned one of five occupational exposure bands, ranging from A through E. These bands, or OEBs, define the range of air concentrations expected to protect worker health for each health endpoint. Band E represents the lowest exposure concentration range recommendation, whereas band A represents the highest exposure concentration range. This is similar to the concept of occupational exposure limits (OEL), where the limit is set based on health information, with more potent/toxic chemicals having OELs set at lower concentrations, while less toxic chemicals have OELs set at higher concentrations. Similarly, occupational exposure bands that represent lower exposure ranges (e.g., band E) are assigned to more potent/toxic chemical substances than bands that represent higher exposure ranges (e.g., band A).

	A	B	C	D	E
Particulate/Dust Gas/Vapor	>10 mg/m³ >100 ppm	>1 to 10 mg/m³ >10 to 100 ppm	>0.1 to 1 mg/m³ >1 to 10 ppm	>0.01 to 0.1 mg/m³ >0.1 to 1 ppm	≤0.01 mg/m³ ≤0.1 ppm

Table 1. Occupational exposure banding concentration ranges.

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

NIOSH Tier 1 Criteria	C	D	E
Exposure ranges			
Dust/particle	>0.1 to ≤1 mg/m³	>0.01 to ≤0.1 mg/m³	≤0.01 mg/m³
Gas/vapor	>1 to ≤10 ppm	>0.1 to ≤1 ppm	≤0.1 ppm
Carcinogenicity	—	—	H350, Category 1, 1A, or 1B
	—	—	H351, Category 2
Reproductive toxicity	H361, Category 2	H360, Category 1B	H360, Category 1 or 1A
Specific target organ toxicity-repeated exposure	H371, Category 2	—	H370, Category 1
	H373, Category 2	—	H372, Category 1
Genotoxicity	—	H341, Category 2	H340, Category 1, 1A or 1B
Respiratory and skin sensitization	H317, Category 1B (skin)	H317, Category 1 or 1A	—
	H335, Category 3	H334, Category 1B	H334, Category 1 or 1A
Acute toxicity	H301, Category 3	H300, Category 2	H300, Category 1
	H302, Category 4	H300, Category 2	H300, Category 1
	H331, Category 3	H330, Category 2	H330, Category 1
	H332, Category 4	H330, Category 2	H330, Category 1
	H311, Category 3	H310, Category 2	H310, Category 1
	H312, Category 4	H310, Category 2	H310, Category 1
Skin corrosion/ irritation	H315, Category 2	—	H314, Category 1, 1A, 1B, or 1C
Eye damage/ irritation	H319, Category 2, 2A or 2B	—	H318, Category 1

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

Abbreviations: mg/m³ = milligrams per cubic meter; ppm = parts per million

Table 2. Tier 1 Occupational Exposure Banding Criteria

Problem
Although occupational exposure banding is useful for chemicals with sufficient data, there are many chemicals in commerce with sparse or no toxicity data. Occupational exposure banding would not work for those chemicals, as there is a minimum data set requirement. NIOSH is beginning to envision an Occupational Exposure Banding 2.0, which would expand the applicability of banding to chemicals with insufficient data for the current banding protocol. Potential avenues of exploration include use of quantitative structure activity relationships (QSAR) and read-across methods. The first step in expanding the banding protocol is describing the potential methods that could be used with chemicals that have little data, including the advantages and disadvantages and inherent uncertainties of the methods. For this preliminary case study, NIOSH is soliciting input on the utility and feasibility of using

a) QSAR in general and specific QSAR methods that have been developed
b) Read-across in general and specific read-across methods that have been developed

to expand occupational exposure banding methods to chemicals without sufficient data for the current banding protocol. Discussion of the strengths, weaknesses and uncertainties resident in such approaches would be especially helpful. NIOSH is also soliciting input on how best to use such techniques, whether as a method to refine Tier 1 or Tier 2 banding results to fill in gaps, or to only use such techniques when there is insufficient data to establish an occupational exposure band.

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2. Describe the problem formulation(s) the case study is designed to address. How is the method described in the case useful for addressing the problem formulation?

The envisioned *Occupational Exposure Banding 2.0* would be designed to address situations where an occupational exposure limit or occupational exposure band is needed, but the chemical-specific data are insufficient to support use of the *NIOSH Occupational Exposure Banding* protocol. This problem would be addressed by expanding the available range of approaches for assessing data-poor chemicals with QSAR approaches and/or read-across methods.

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The vast majority of chemicals in commerce have no occupational exposure limits and little toxicity data. NIOSH has addressed a portion of this problem with the occupational exposure banding tool. However, a minimum array of available data is necessary to support banding. For those chemicals with insufficient data to support an occupational exposure band, the banding tool does not offer guidance ~~on controlling exposures~~estimating reasonable OELs or OEBs. Some suggestions from stakeholders have included using a precautionary principle and assuming that every chemical is band E (most toxic) until sufficient data is available for banding. Or, alternatively, by assuming band C (medium toxicity) until sufficient data are available to better understand the risks. The problems with those assumptions arise when the actual toxicity does not match the assumption. The presumption of high toxicity can lead employers away from less toxic substitutes and the presumption of medium or low toxicity can lead employers to a false sense of safety for more toxic chemicals.

Much work has been done recently to modernize and standardize read-across and QSAR methods. NIOSH is interested in determining whether use of those types of protocols would be reliable indicators of toxicity, whether they would work better for certain classes of chemicals, and how the processes could be standardized to produce reliable toxicity assessments for chemicals with little to no toxicity data. Of particular interest is how to incorporate toxicity data on the chemical in question with predictions from a read across or QSAR method. In addition, understanding the limitations and uncertainties associated with these approaches, and how best to evaluate the method(s) for reliability of toxicity predictions, would be helpful.

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Chemical:	Dimethyl-chickenwire							
CAS Number:	000-00-0							
Endpoint/Toxicity parameter		**Most conservative band represented by the data**					**Determinant Score**	**Endpoint-specific band selection**
(Score for the presence of data)		**A**	**B**	**C**	**D**	**E**		
Cancer potential	WOE (U.S. EPA)						0	
(20 for qualitative info, 30 for quantitative)	SF (U.S. EPA)			C			30	C
Determinant sub-score (cancer)							**30**	
Reproductive (30)			C				**30**	C
Target organ toxicity (repeat exposure)	RfD (U.S. EPA)				D		30	D
Determinant sub-score (systemic toxicity)							**30**	
Mutagenicity (in vivo) (10)					D		**10**	D
Mutagenicity (in vitro) (5)				C			**5**	C
Respiratory sensitization (10)							**0**	
Skin sensitization (5)				C			**5**	C
Acute Toxicity (5)	LD_{50} (oral)		B				5	B
Determinant sub-score (acute toxicity)							**5**	
Skin irritation/corrosion (5)			B				**5**	B
Eye irritation/corrosion (5)			B				**5**	B
TDS (Threshold for sufficient data = 30)							**125**	Yes, assign Tier 2 band
Tier 2 Band selection								**D**

Table 3. Sample occupational exposure banding score sheet.

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3. **Comment on whether the method is general enough to be used directly, or if it can be extrapolated, for application to other chemicals and/or problem formulations. Please explain why or why not.**

We envision this method would be useful for preliminary classification of toxicity in order of magnitude toxicity bands. This information could ideally then be used by employers to prioritize chemicals, select potential substitutes and to set internal controls to reduce exposures to employees to safer levels, based on a rational assessment of the totality of information, including chemical structure, chemical class, and analogy to chemicals of known toxicity.

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4. **Discuss the overall strengths and weaknesses of the method.**

There are always uncertainties when basing decisions on incomplete data. The potential strength of this method is in maximizing the utility of information about chemical structure, class, and functional groups in order to make the best decisions in the absence of complete data. The greatest potential weaknesses are that there is insufficient information available to reliably predict a toxicity band, or that alternative approaches using incomplete information lead to disparate results. Evaluation of the reliability of the method would be a critical step. NIOSH solicits suggestions on approaches for assessing and comparing the reliability of different methods (QSAR and read-across, for example) for establishing occupational exposure bands in the absence of sufficient data are requested. In addition, suggestions on determining the minimum data requirements and their contributions to ensuring confidence in the method and its output are requested.

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5. **Outline the minimum data requirements and describe the types of data sets that are needed.**

Ideally, a method would be developed that could work based on chemical structure, so the data set needed for an individual chemical of interest would be small ~~for the subject chemicals~~. The approach could be limited to certain classes of chemicals. Some thought ~~would be helpful~~ around ~~trying~~ how best to define the minimum data needed to establish the chemicals of known toxicity to use as comparators in either the QSAR or read-across methods would be helpful. In addition, discussion of the parameters around how to define a chemical of sufficient "closeness" in structure or chemical class in order to accurately predict toxicity, ideally with a statistical or other objective test to use as a criteria for when it would be acceptable to use the method.

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Does your case study:

A. **Describe the dose-response relationship in the dose range relevant to human exposure?**

These methods are not looking at quantitative dose-response relationships directly.

B. **Address human variability and sensitive populations?**

These methods do not necessarily address concerns about human variability and sensitive subpopulations directly.

C. Address background exposures or responses?

These methods do not address background exposures or responses.

D. Address incorporation of existing biological understanding of the likely mode of action?

It is anticipated that the eventual selected methods or approaches to enhance the occupational exposure banding protocol (for example, QSAR or read-across) would incorporate information on mode of action for the chemicals of known toxicity and some method of assessing how likely the subject chemical is to have the same or similar mode of action.

E. Address other extrapolations, if relevant – insufficient data, including duration extrapolations, interspecies extrapolation?

These methods are specifically designed to address the case of insufficient data on toxicity and how to ameliorate that situation.

F. Address uncertainty?

These methods should give the user a full understanding of the inherent uncertainties in predicting toxicity based on chemical structure, chemical class or functional groups.

G. Allow the calculation of risk (probability of response for the endpoint of interest) in the exposed human population?

These methods are not designed to calculate risk, but to give an order of magnitude assessment of the toxicity of airborne concentrations of the subject chemicals.

H. Work practically? If the method still requires development, how close is it to practical implementation?

This method requires development and evaluation of the utility. It is not close to practical implementation at this time.

References

NIOSH [2019]. Technical report: The NIOSH occupational exposure banding process for chemical risk management. By Lentz TJ, Seaton M, Rane P, Gilbert SJ, McKernan LT, Whittaker C. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2019-132, https://doi.org/10.26616/NIOSHPUB2019132external icon

Questions for the panel:

1. Which quantitative structure-activity relationships (QSAR) methods would you recommend as a starting place for developing a predictive banding protocol?
    a. Is this method of sufficient maturity and complexity that it would provide a reasonable estimate of the toxicity across all nine endpoints?
    b. Are there some endpoints that are problematic? Why?
    c. What are the major uncertainties associated with this method? How can they be overcome?
    d. What is the range of chemical structures that could be accommodated by this method?
    e. What other advantages and disadvantages are there to this method?
2. Are there other QSAR methods NIOSH should consider? Please elaborate on the questions above for those methods.
3. Which read-across methods would you recommend as a starting place for developing a predictive banding protocol?
    a. Is this method of sufficient maturity and complexity that it would provide a reasonable estimate of the toxicity across all nine endpoints?
    b. Are there some endpoints that are problematic? Why?
    c. What are the major uncertainties associated with this method? How can they be overcome?
    d. What is the best way to define the range of chemicals that a read-across method would reliably predict toxicity?
    e. What is the minimum data required for reliable extrapolation of toxicity?
    f. How is the "relatedness" of the chemical defined? What considerations should be taken into account when NIOSH selects chemicals to define a class for read-across?

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