EPA's New Chemicals Program under TSCA
Standardized Approach for Mixed Metal Oxides (MMOs) in Cathode Active Materials (CAMs) and Modified CAMs

Webinar Series: Part 2

March 30, 2023

Agenda

- Background
- Details of standardizing the human health risk assessment process for MMOs/CAMs
  - General Approach
  - Decision Framework
  - Points of Departure (PODs)
  - Spreadsheet results

Background

- Kick-Off webinar was presented November 17, 2022
- Discussed the following:
  - TSCA section 5 regulation of Mixed Metal Oxides (MMOs) including Cathode Active Materials (CAMs) as stated in the October 2022 Compliance Advisory
  - Steps for navigating the new submission process, including in relation to the TSCA Inventory, Nomenclature, and the Bona Fide process.
  - Introduction to EPA's initiative to standardize new chemical reviews for MMOs, including CAMs
- Additional information on this approach can be located on EPA's webpage

  Integrated Approach for Mixed Metal Oxides New Chemical's Review

General Approach

- This approach focuses on one of the most time consuming parts of the new chemical review process for MMOs CAMs: the human health risk assessment

Risk Assessment Overview

Understanding the Chemical

- Chemistry
- Environmental Fate
- Environmental Release

Understanding Exposure

- Occupational
- General Population
- Consumers
- Environmental Organisms

Understanding Hazard

- Human Health
- Environmental Organisms

Determining Risk

- Human Health
- Environmental Organisms

Risk = Hazard x Exposure

- New Chemicals Program follows EPA Guidance for Risk Assessment
- OPPT has longstanding practices and procedures
- Examine variety of exposure scenarios at each step in life cycle
- For risks to humans, look at:
  - Risk to workers, general population, and consumers
  - Risk through dermal, oral (drinking water and fish ingestion), and inhalation routes
  - Cancer and non-cancer
- Use most conservative exposure scenario to calculate the risk estimates
- Compare risk to benchmarks to understand unreasonable risk, for example:
  - For general population cancer risk, use 1 in 1,000,000 (1×10^{-6})

General Approach – Key Factors

- Determination of bioavailability
- Use of a component-based approach for MMOs
- Sources of hazard information
- Derivation of Points of Departure
- Use of a risk calculator

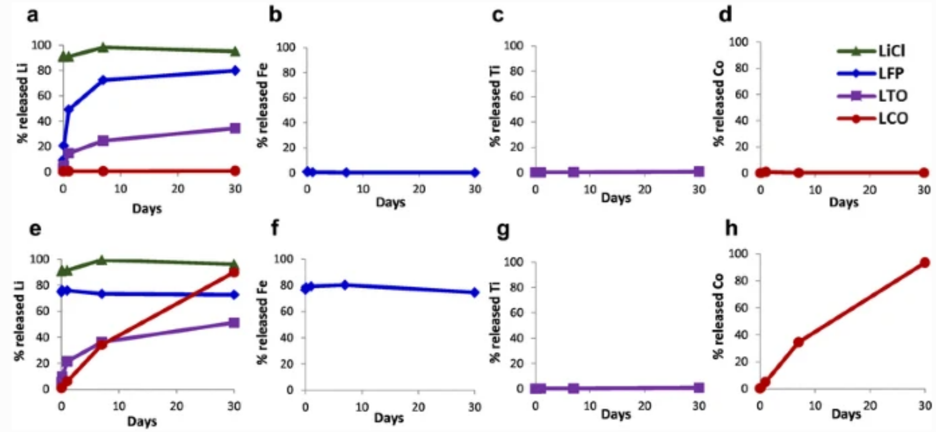
General Approach

- This approach applies to CAMs that are MMOs typically reviewed by EPA as respirable, poorly soluble particulates according to the TSCA New Chemicals Category Document (2010).
- **Industry has provided a list of example metals likely to be used. To support efficient and timely risk assessments, EPA used the information in this list to develop a scientifically robust approach to assess risks for MMOs used as CAMs *before* receiving the new chemical submissions.**
- **Since this approach has been developed based on EPA's experience with previously submitted CAMs and the expectation is that the new chemical submission will be doped with a narrow subset of metals**, the first step in this approach is to compare the new chemical substance with past submissions to determine if the submission is appropriately similar based on the metal composition and the physicochemical properties (e.g., high molecular weight, poorly soluble, no nano-sized particles).

General Approach

- Bioavailability:
  - **Individual metal components are assumed to be completely bioavailable**
  - Supported by TSCA CBI data and publication by Sironval et al., 2018 (see excerpted Fig. 1)

Fig. 1



Bioaccessibility of constitutive elements from LIB particles. LIB particles and LiCl were incubated in artificial fluids mimicking the extracellular (pH 7.3) (**a–d**) and the phagolysosomal (pH 4.2) (**e–h**) compartments. Particles were incubated at 37 °C under gentle agitation and released Li (**a, e**), Fe (**b, f**), Ti (**c, g**) and Co (**d, h**) concentrations were determined by ICP-MS in the SN after centrifugation of an aliquot of the suspensions after 3 h, 24 h, 7 days and 30 days

Sironval, V., Reylandt, L., Chaurand, P. *et al.* Respiratory hazard of Li-ion battery components: elective toxicity of lithium cobalt oxide ($LiCoO_2$) particles in a mouse bioassay. *Arch Toxicol* **92**, 1673–1684 (2018). https://doi.org/10.1007/s00204-018-2188-x

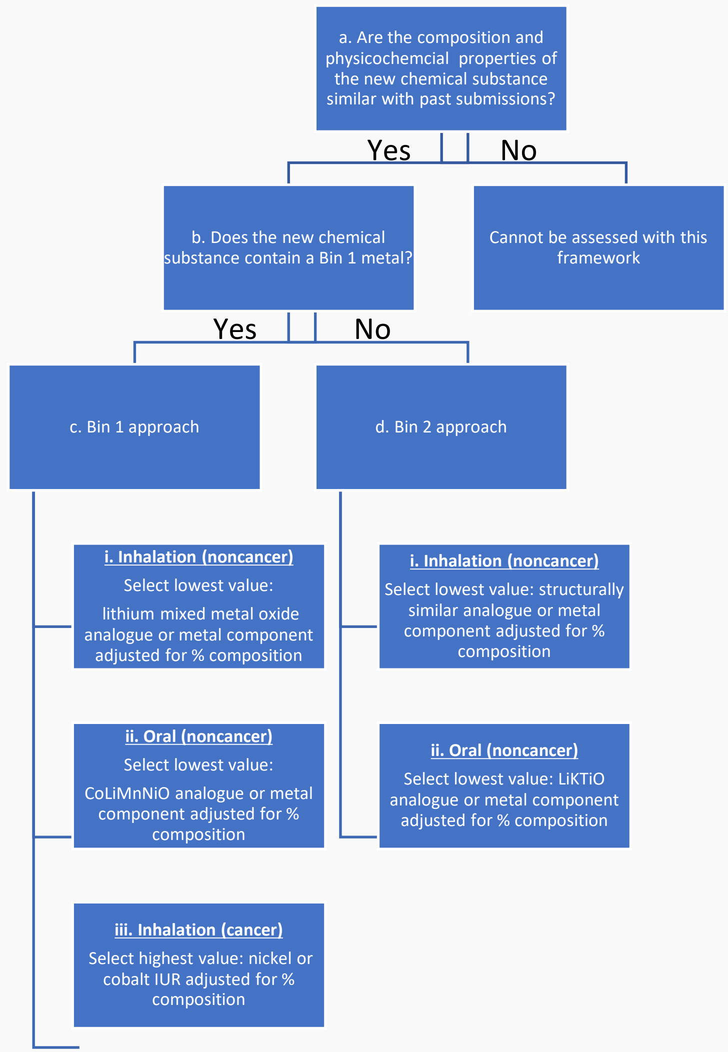
General Approach

- Component-Based Approach:
  - An additive approach was not considered appropriate to assess CAMs since this would compound conservatism. The approach already assumes that each metal is completely bioavailable, which is a conservative assumption based on the available data.
  - In addition, the metal composition is typically variable for these submissions with the high-end estimates of the metal oxide components sometimes exceeding 100% (e.g., Lithium: 2-70%, Cobalt: 5-70%, Nickel: 50-99%).
  - Since EPA defaults to the high-end estimate for each component to assess risk, an additive approach would overestimate risk.
  - To avoid excessively compounding conservative estimates, EPA evaluated the individual toxicity of each component and compared it to the MMO analogues with repeated-dose data historically used in the New Chemicals Program.

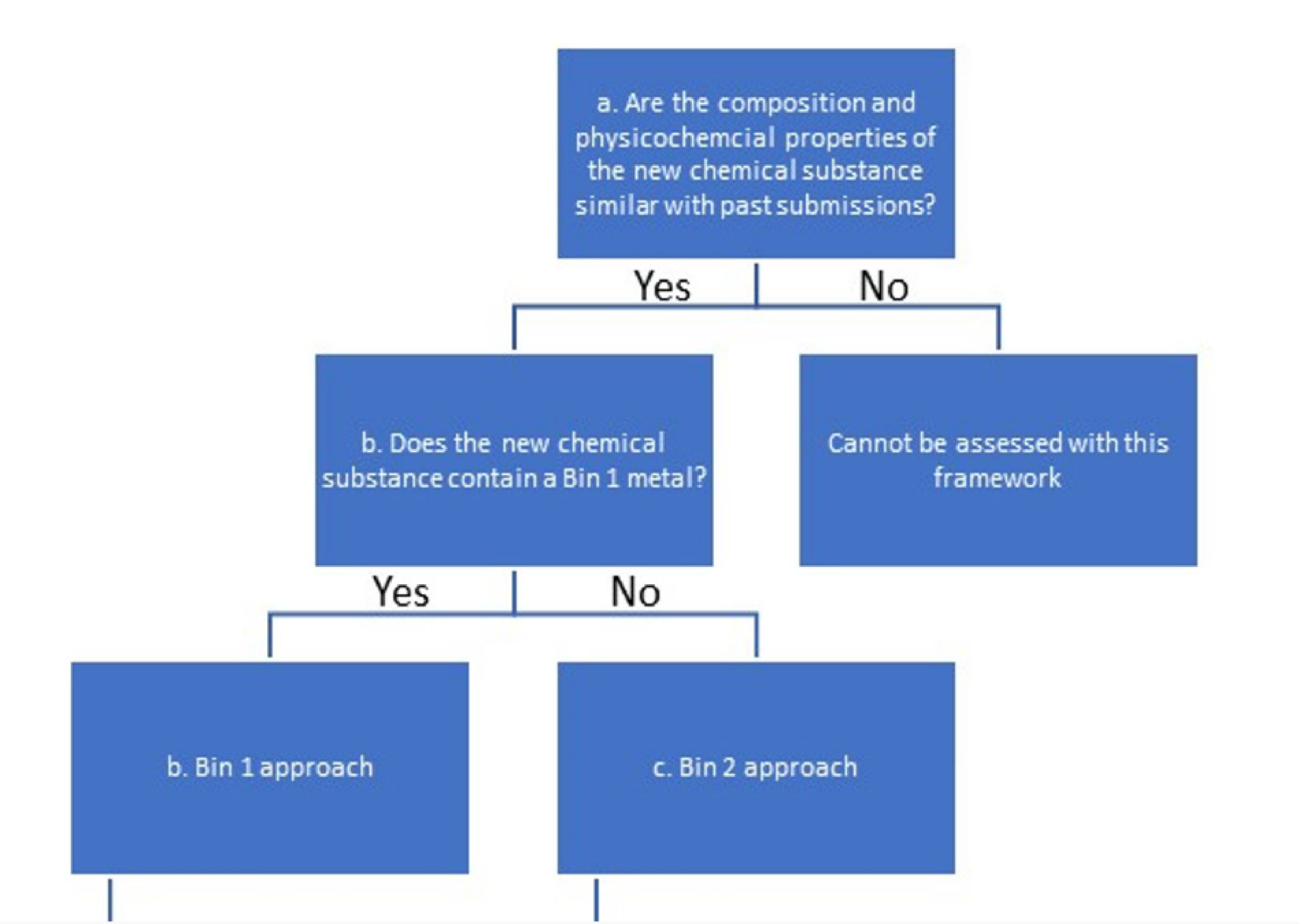
General Approach

- Sources for hazard information:
  - For nearly all the identified individual metals, a risk assessment by an authoritative regulatory body is available.
  - EPA also has several high-quality, TSCA CBI, 90-day inhalation studies on MMOs of various compositions which have previously been used to quantitatively assess lung effects.
  - MMOs are expected to be insoluble, thus the POD for the insoluble form of the metal component was selected, if available.
  - When an insoluble POD was not available, the soluble POD, as in the case of tungsten, was selected with the assumption that the soluble POD is the more health protective option.

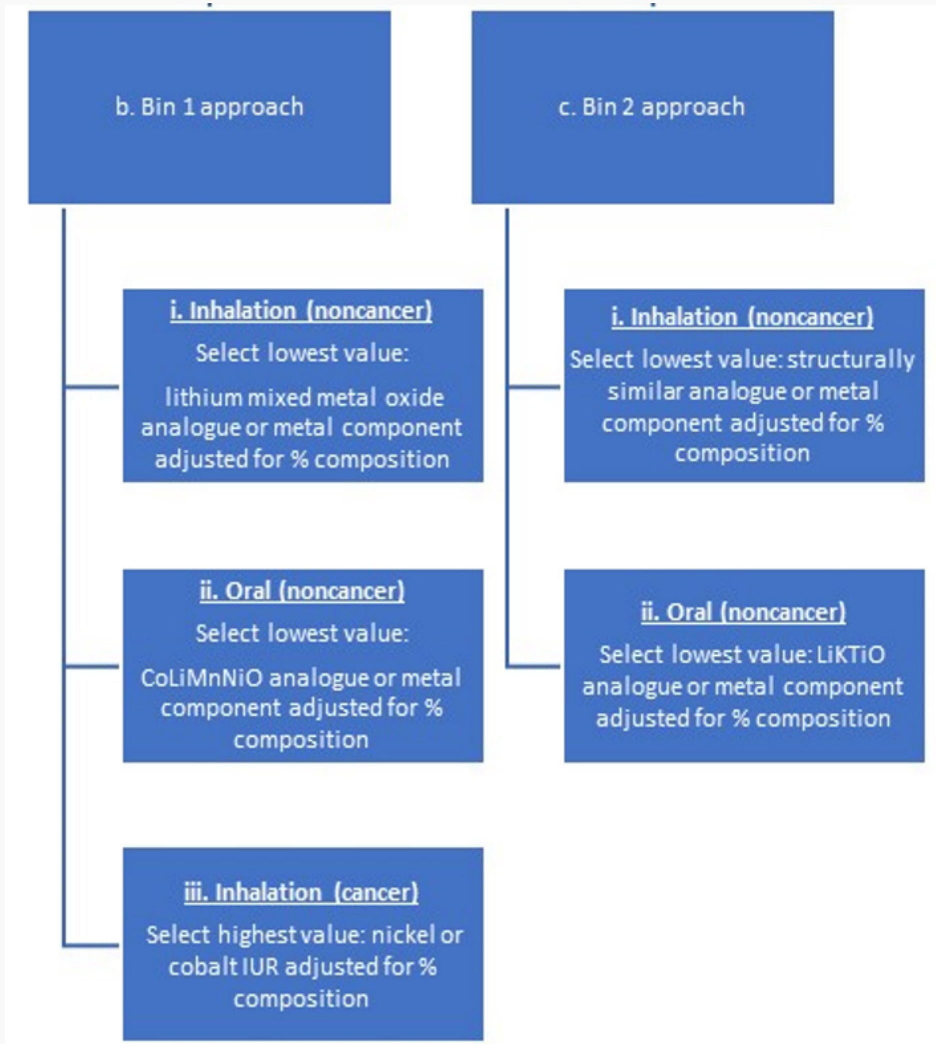
Deriving the points of departure



Deriving the points of departure



Deriving the points of departure



PODs for CAM metals (Bin 1)

Metal		Inhalation Unit Risk	Oral POD	Inhalation POD
Cobalt	Value	7.7e-3 $(\mu g/m^3)^{-1}$	LOAEL: 1 mg/kg-bw/day Total UF: 100 (10 UF_L, 10 UF_H)	NOAEC: 5.3e-3 mg/m^3 Total UF: 10 (UF_H)
	Critical effect	Lung cancer	Systemic effects	Respiratory effects
	Study	Rat and mouse 2-year inhalation exposure	2-week human exposure	Human cross-sectional study
	Source	OEHHA	PPRTV	PPRTV[6]
Nickel	Value	2.6e-4 $(\mu g/m^3)^{-1}$	NOAEL: 1.12 mg/kg-bw/day Total UF: 100 (10 UF_A, 10 UF_H)	BMCL: 1.17e-1 mg/m^3 Total UF: 100 (10 UF_A, 10 UF_H)
	Critical effect	Lung cancer	Reproductive effects	Respiratory effects
	Study	Human worker exposure	Rat 2-generation oral gavage exposure	Mouse 104-week inhalation exposure
	Source	OEHHA	OEHHA	OEHHA[8]
CoLiMnNiO	Value	N/A	NOAEL: 15 mg/kg-bw/day Total UF: 100 (10 UF_A, 10 UF_H)	LOAEC: 0.28 mg/m^3 Total UF: 1000 (10 UF_A, 10 UF_H, 10 UF_L)
	Critical effect		Systemic effects	Respiratory effects
	Study		Rat 28-day oral gavage exposure	Rat 90-day inhalation exposure
	Source		CBI submitted study	CBI submitted study
Lithium mixed metal oxide	Value	N/A	N/A	BMCL: 8.4e-3 mg/m^3 Total UF: 100 (10 UF_A, 10 UF_H)
	Critical effect			Respiratory effects
	Study			Rat 90-day inhalation exposure
	Source			CBI submitted study

PODs for CAM metals (Bin 2)

Metal		Oral POD	Inhalation POD
Zirconium	Value	LOAEL: 0.79 mg/kg-bw/day Total UF: 1000 (10 UF_A, 10 UF_H, 10 UF_L)	N/A
	Critical effect	Systemic effects	
	Study	Rat lifetime drinking water exposure	
	Source	PPRTV	
Boron	Value	BMDL: 10.3 mg/kg-bw/day Total UF: 66	N/A
	Critical effect	Developmental effects	
	Study	Rat dietary gestational exposure	
	Source	IRIS	
Tungsten	Value	BMDL: 2.3 mg/kg-bw/day Total UF: 100 (10 UF_A, 10 UF_H)	N/A
	Critical effect	Systemic effects	
	Study	Rat 90-day oral gavage exposure	
	Source	PPRTV	
Aluminum	Value	NOAEL: 30 mg/kg-bw/day Total UF: 100 (10 UF_A, 10 UF_H)	LOAEC: 1.64 mg/m^3 Total UF: 100 (10 UF_L, 10 UF_H)
	Critical effect	Systemic effects	Systemic effects
	Study	Rat 1-year drinking water exposure	Human worker inhalation exposure
	Source	JECFA	PPRTV
Lithium	Value	LOAEL: 2.1 mg/kg-bw/day TotaL: 100 (10 UF_H, 10 UF_L)	N/A
	Critical effect	Systemic effects	
	Study	Human exposures	
	Source	PPRTV	

Metal		Oral POD	Inhalation POD
Manganese	Value	LOAEL: 25 mg/kg-bw/day Total UF: 1000 (10 UF_A, 10 UF_H, 10 UF_L)	$LOAEL_{HEC}$: 0.05 mg/m^3 Total UF: 100 (10 UF_H, 10 UF_L)
	Critical effect	Systemic effects	Systemic effects
	Study	Rat oral exposure (multiple studies)	Human occupational exposure
	Source	WHO	IRIS
Titanium	Value	N/A	NOAEC: 10 mg/m^3 Total UF: 100 (10 UF_H, 10 UF_A)
	Critical effect		Respiratory effects
	Study		Rat 2-year inhalation exposure
	Source		NICNAS
Magnesium		Low hazard	N/A
Niobium		Low hazard	N/A
LiKTiO	Value	NOAEL: 50 mg/kg-bw/day Total UF: 100 (10 UF_H, 10 UF_A)	N/A
	Critical effect	Systemic effects	
	Study	Rat 28-day oral gavage exposure	
	Source	ECHA	
LiMnO	Value	N/A	NOAEC: 4 mg/m^3 Total UF: (10 UF_H, 10 UF_A)
	Critical effect		Respiratory effects
	Study		Rat 90-day inhalation exposure
	Source		US EPA
KTiO	Value	N/A	NOAEC: 10 mg/m^3 Total UF: (10 UF_H, 10 UF_A)
	Critical effect		Respiratory effects
	Study		Rat 90-day inhalation exposure
	Source		CBI submitted study

Exposure routes of interest

- The proposed approach assumes that the individual metal components are completely **bioavailable following either oral or inhalation exposures**.
- Due to the large molecular weight and negligible water solubility, dermal absorption is expected to be nil through the skin, therefore systemic effects are not expected via dermal exposure and risks will not be quantified for dermal exposures. However, analogue data for MMOs that contain cobalt or nickel are positive for skin sensitization in submitted studies.
- **EPA will qualitatively evaluate skin sensitization via dermal exposures**.

Risk Calculator

- Demonstration

Calculating Risk: Exposure Data Entry

Worker Exposure Summary from Engineering Assessments							
Scenario	Number of Workers Exposed	Inhalation Exposure		Dermal Exposure		Activity	Key Notes for Basis of Estimates
		PDR (mg/day)	LADD (mg/kg-day)	PDR (mg/day)	LADD (mg/kg-day)		
Manufacturing	10	2.40E-01	1.10E-03	2.00E+03	5.00E+00	Loading Solid Product into Transport Containers	Inhalation estimate based on monitoring data
Use	3	2.40E-01	1.10E-03	1.50E+03	1.00E+00	Disposal of collected waste	Inhalation estimate based on small volume model

NCEM2 Results Table: General Population Exposure Summary from Exposure Assessments														
Scenario	Drinking Water		Fish Ingestion		Landfill		Stack Air Dose		Stack Air Conc.		Fugitive Air Dose		Fugitive Air Conc.	
	ADR (mg/kg/day)	LADD (mg/kg/day)	ADR (mg/kg/day)	LADD (mg/kg/day)	ADD (mg/kg/day) = 2.36 x LADD	LADD (mg/kg/day)	ADR (mg/kg/day)	LADD (mg/kg/day)	24-hr conc. (µg/m3)	Annual conc. (µg/m3)	ADR (mg/kg/day)	LADD (mg/kg/day)	24-hr conc. (µg/m3)	Annual conc. (µg/m3)
MFG	1.07E-02	9.02E-05	n/a	n/a	5.19E-03	2.20E-03	5.27E-05	4.29E-06	2.90E-01	5.54E-02	1.20E-01	3.38E-03	6.80E+02	4.37E+01
PROC	8.38E-02	3.92E-03	n/a	n/a	9.53E-04	4.04E-04	3.70E-01	3.02E-02	2.44E+03	3.90E+02	2.40E+00	7.82E-02	1.31E+04	1.01E+03
USE	1.30E-02	2.97E-04	n/a	n/a	1.08E-03	4.59E-04	2.25E-05	8.90E-07	1.20E-01	1.15E-02	9.19E-03	1.17E-04	5.02E+01	1.51E+00
Highest Exposure Value	8.38E-02	3.92E-03	0.00E+00	0.00E+00	5.19E-03	2.20E-03	3.70E-01	3.02E-02	2.44E+03	3.90E+02	2.40E+00	7.82E-02	1.31E+04	1.01E+03

Calculating Risk: Human Health Data Entry

- Determine if the new chemical substance contains a Bin 1 metal.
- Input the percent composition of the metal components into the spreadsheet according to the decision framework

Bin 1

Enter Metal Composition

Metal	**% composition**
Cobalt	25%
Nickel	30%

Bin 2

Enter Metal Composition

Metal	**% composition**
Zirconium	0.00%
Boron	0.00%
Tungsten	0.00%
Aluminum	3.60%
Lithium	75.00%
Manganese	24.00%
Titanium	0.00%
Magnesium	0.00%
Niobium	0.00%

Example Results: Hazard Summary

EPA estimated the human health hazard of this chemical substance based on its estimated physical/chemical properties, by comparing it to a structurally analogous chemical substance for which there is information on human health hazard, and other structural information. Absorption of the new chemical substance is expected to be nil via the lung and dermal routes and poor by the GI tract based on physical/chemical properties. Based on test data for analogues, the metal components in the new chemical substance are expected to be bioavailable following inhalation and oral exposures.

For the new chemical substance, EPA identified hazards for carcinogenicity, genetic toxicity, skin sensitization, respiratory sensitization, reproductive, systemic, and respiratory effects based on analogue data. EPA identified an IUR of 7.7e-3 (µg/m3)-1 based on lung cancer, a LOAEL of 1 mg/kg-bw/day based on systemic effects and a BMCL of 8.4e-3 mg/m3 based on respiratory effects which was protective for carcinogenicity, reproductive, systemic, and respiratory effects. EPA qualitatively evaluated sensitization effects.

Example Results: Risk Statements (Workers)

Worker Risks

Manufacturing

Risks were identified for lung effects for workers based on quantitative hazard data for a component of the new chemical substance.

MOE = 1.29E-03 Fold Factor = 777

Cancer risks for workers via inhalation exposures were calculated based on quantitative hazard information for a component of the new chemical substance.

Cancer risks= 1.81E-02

Target risk	Fold Factor
1.0E-04	180.9192
1.0E-05	1809.192
1.0E-06	18091.92

Example Results: Risk Statements (General Population Drinking Water)

MANUFACTURING	USE	PROCESSING
Risks were not identified for systemic effects for the general population via drinking water exposure based on quantitative hazard data for a component of the new chemical substance.	Risks were not identified for systemic effects for the general population via drinking water exposure based on quantitative hazard data for a component of the new chemical substance.	Risks were not identified for systemic effects for the general population via drinking water exposure based on quantitative hazard data for a component of the new chemical substance.
MOE =2.50E+00	MOE =1.58E+01	MOE =2.06E+00
Risks were identified for systemic effects for the general population (infants) via drinking water exposure based on quantitative hazard data for a component of the new chemical substance.	Risks were identified for systemic effects for the general population (infants) via drinking water exposure based on quantitative hazard data for a component of the new chemical substance.	Risks were not identified for systemic effects for the general population (infants) via drinking water exposure based on quantitative hazard data for a component of the new chemical substance.
MOE =5.95E-01	MOE =4.90E-01	MOE =3.77E+00

Example Potentially Useful Information (Section 1.4)

- EPA lists in this section testing information that would be helpful for the human health risk assessment.
- Example testing recommendations:
  - Biosolubility (all submissions)
  - Specific Target Organ Toxicity (all submissions)
  - Reproductive Toxicity (only for MMOs that contain cobalt, nickel, boron, or lithium)
  - Genetic Toxicity (only for MMOs that contain cobalt or nickel)
  - Skin Sensitization (only for MMOs that contain cobalt or nickel)
  - Pulmonary Effects (all submissions)

Example Hazards (Section 1.5)

- Cobalt: Carcinogenicity, Genetic Toxicity, Skin Sensitization, Respiratory Sensitization, Reproductive Toxicity, Specific Target Organ Toxicity
- Nickel: Carcinogenicity, Genetic Toxicity, Skin Sensitization, Reproductive Toxicity, Specific Target Organ Toxicity
- Zirconium: Specific Target Organ Toxicity
- Boron: Specific Target Organ Toxicity, Reproductive Toxicity
- Manganese: Specific Target Organ Toxicity
- Lithium: Specific Target Organ Toxicity, Reproductive Toxicity
- Tungsten: Specific Target Organ Toxicity
- Aluminum: Specific Target Organ Toxicity
- Titanium: Specific Target Organ Toxicity
- Magnesium: None
- Niobium: None

Conclusions

- This standardized CAMs approach ensures EPA's risk assessment is consistent, efficient and transparent.
- Decision tree framework and risk calculators are tools submitters can use to better the potential risk of their CAM/modified CAM and what information is needed before they submit their pre-manufacture notice.
- Note: This approach may be updated in the event EPA receives new information from submitters, or if the science on this evolves.

Additional Resources

- Points of Contact
  - Inventory (Tracy Williamson – Williamson.tracy@epa.gov)
  - Risk Assessment (Keith Salazar – Salazar.Keith@epa.gov)
  - Risk Management (Jim Alwood – Alwood.jim@epa.gov)

- Additional Information
  - Standardized Approach for Mixed Metal Oxides New Chemicals Review Training/Outreach
  - TSCA Compliance Advisory issued in October 2022
  - New Chemicals Review Process under TSCA
  - TSCA Inventory and Bona Fide Process (40 CFR 720.25)
  - Applicable Regulations for Premanufacture Notice (40 CFR 720) and Significant New Use Notice and Rules (40 CFR 721)
  - EPA's "Points to Consider When Preparing TSCA New Chemical Notifications"
  - Information about Filing a Premanufacture Notice