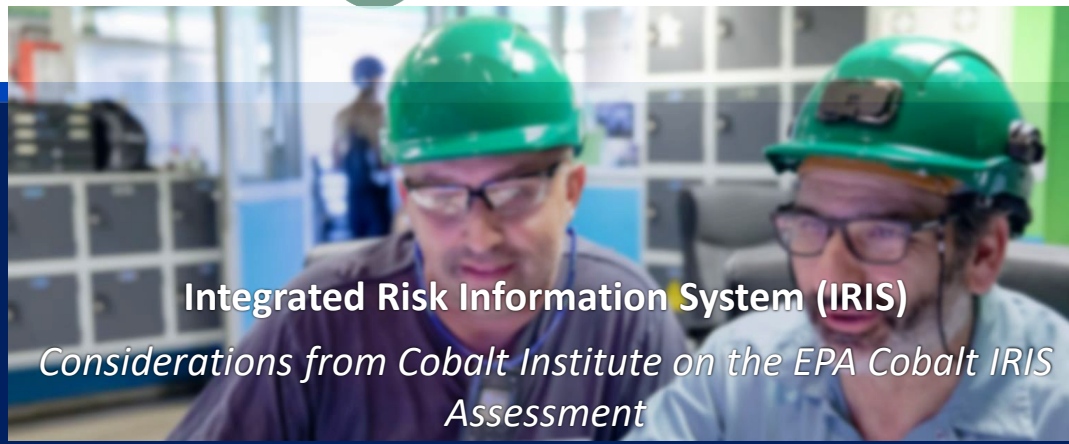

Integrated Risk Information System (IRIS)

Considerations from Cobalt Institute on the EPA Cobalt IRIS Assessment

Monday, 6th November 2023

Andrew Maier, ChemRisk/Stantec, Principal Health Scientist
Lynne Marshall, ChemRisk/Stantec, Supervising Health Scientist
Marisa Kreider, ChemRisk/Stantec, Principal Health Scientist
Vanessa Viegas, Cobalt Institute, Deputy Head of Scientific and Regulatory Affairs & Principal Toxicologist (Human Health)

Agenda And Presenters

Introduction		
3:00 – 3:10 pm **(10 mins)**	*Participant Introductions* *Background on Cobalt Institute*	**All** **Vanessa Viegas** – Cobalt Institute
Background on Cobalt and Cobalt Compounds		
3:10 – 3:15 pm **(5 mins)**	*Material flow* *Manufacture, use and exposure* *Cobalt as essential to life, security and green transition*	**Vanessa Viegas** – Cobalt Institute
Cobalt Institute Data and Approaches		
3:15 – 3:35 pm **(20 mins)**	*Grouping and read-across data – in vitro, in vivo, MoA* *Addressing key scientific questions* *New data to be generated by CI in next 4+ years*	**Vanessa Viegas** – Cobalt Institute **Marisa Kreider** – Stantec/ChemRisk **Andrew Maier** – Stantec/ChemRisk
Epidemiology Data and Comparisons Of Potency		
3:35 – 3:50 pm **(15 mins)**	*Stantec ChemRisk epidemiology data analysis and carcinogenic potency comparisons*	**Lynne Marshall** – Stantec/ChemRisk **Marisa Kreider** – Stantec/ChemRisk **Andrew Maier** – Stantec/ChemRisk
Closing Remarks		
3:50 – 4:00 pm **(10 mins)**	*Questions, discussion, concluding remarks* *(can also be taken with other Agenda Items)*	**All**

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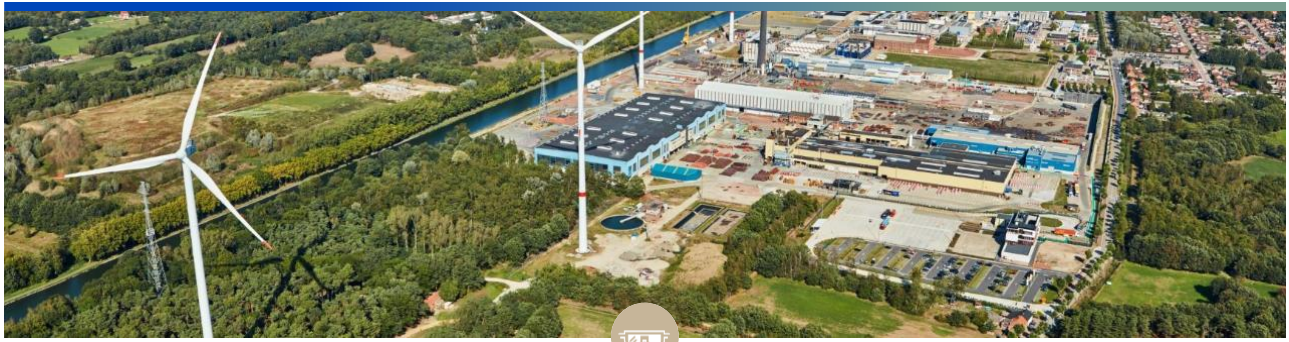

1 – Introduction

Presenters

Vanessa Viegas
Principal
Toxicologist
Cobalt Institute

Marisa Kreider
Principal Health
Scientist
ChemRisk/Stantec

Andrew Maier
Principal Health
Scientist
ChemRisk/Stantec

Lynne Marshall
Supervising Health
Scientist
ChemRisk/Stantec

Cobalt Institute

Global trade association representing the cobalt industry and value chain.

Promotes the sustainable and responsible production and use of cobalt.

Knowledge centre for regulators, governments, industry, NGOs the media and the public.

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CI Members


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BASF
We create chemistry
洛阳钼业
China Molybdenum
CTT
ERG
GLENCORE
CoNiChem
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borchers
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High Performance Metal Solutions
SANDVIK
Shepherd
ALFRED H KNIGHT
AngloAmerican
ATI
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ESPAÑA
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KENNAMETAL
JX Nippon Mining & Metals
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MITSUI & CO.
OCEAN MINERALS
saft
SGS
VENATOR
the metals company
wogen
WESTWIN ELEMENTS
BRAZILIAN NICKEL
CIC
CobaltBlue
Electra
Battery Materials
FORTUNE
USGS
science for a changing world
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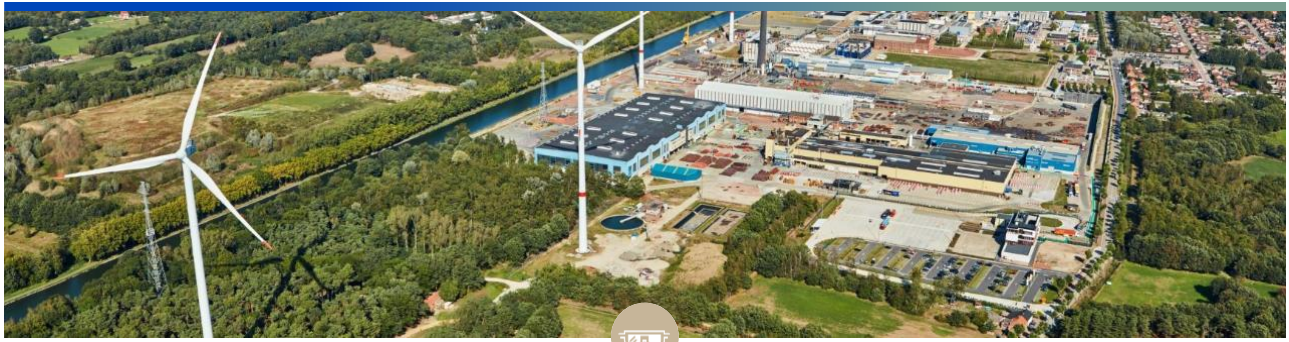

2 – Background on Cobalt and Cobalt Compounds

- *Material flow*
- *Cobalt as essential to life, security and the green transition*
- *Manufacture and use*

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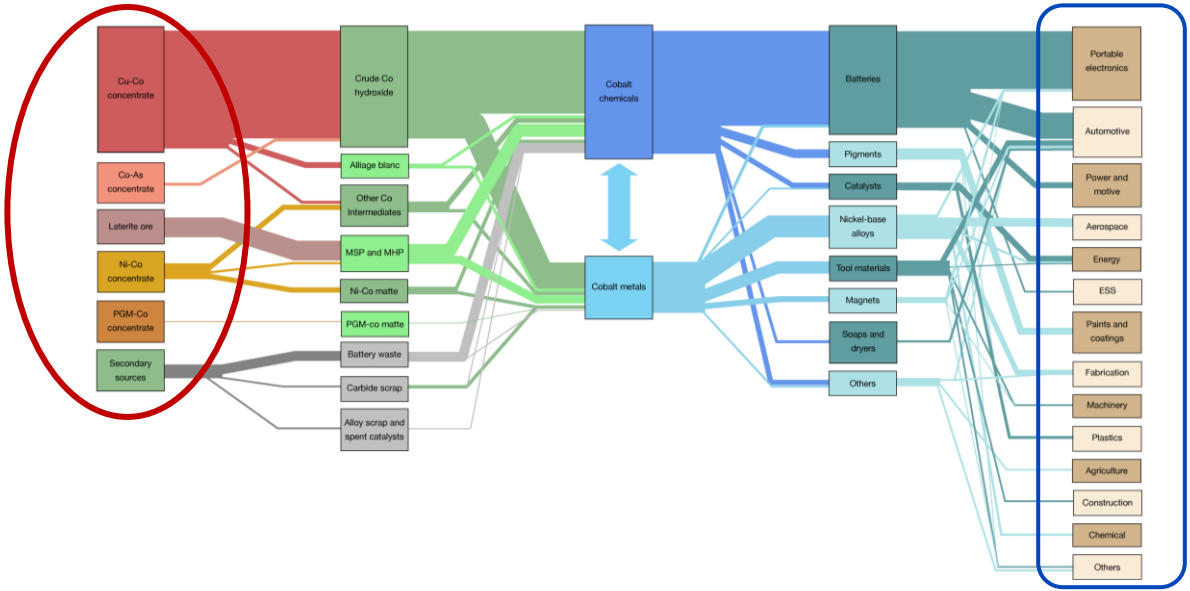
Global Cobalt Value Chain (2021)



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Cobalt Is An Essential Element

Cobalt, as part of vitamin B12 occurs naturally in the tissues of animals and humans

Essential to various bacteria, which utilise cobalt to improve **plant growth**.

Essential for **human health** to maintain healthy red blood cells and nerve cells; brain function and formation of DNA.

= **essential for life**

Cobalt levels in animal- or human tissue can -and must- never be “zero”.

Occurs naturally in rock and soil

Essential to bacteria and core of Vit B12

Transition metal

Common in biology/nature Co^{2+} ion

Essential in many sectors of use!

Unique properties → ***Hazard profile***

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Cobalt Is Essential To Security And The Green Transition

Cobalt in defense

Fighter jets (magnets, sensors and avionics, superalloys)

Naval ships (electric motors, nuclear submarines)

Cobalt in aerospace

Superalloys (jet engine turbines)

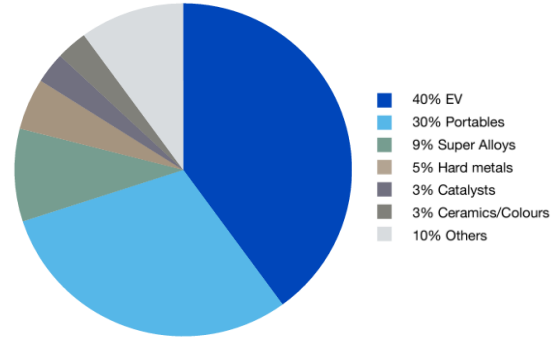
Cobalt in tools

Tungsten carbide tools (drill bits as used in construction etc.)

Cobalt in green technologies

Batteries (NMC, NCA, LCO)

Desulphurisation of petrol and diesel fuel



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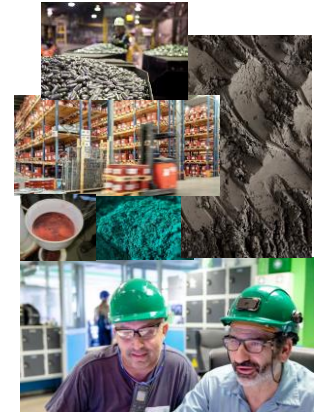
MANUFACTURE AND USE OF COBALT SUBSTANCES

- **Cobalt has been manufactured and used in for over 50 years with safe handling and use.**
- **A variety of risk management measures are already in-place across cobalt workplaces.**
- **Risks from cobalt are more likely associated with workplace exposure.**



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3 – Cobalt Institute Data and Approaches

- *New data to be generated by CI in next 4 – 6 years*
- *Grouping and read-across data – in vitro, in vivo, MoA*
- *Addressing key scientific questions*

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Cobalt Institute – Simplified Database

Toxicology and mode-of-action	Epidemiology	Leading Health effects
Cancer → **NTP rodent studies**	**Cancer** → **Hard metal epidemiology studies; Marsh et al. 2017 etc.**	→ **Lack of cancer in human cohorts, at exposures observed** → **Cancer in rodents, at high exposures (mice and rats)** → **Decrease in lung function (humans)**
Mode-of-action, inhalation toxicity → **CI inhalation 'read across' carcinogenicity prediction**	→ **Sauni et al. 2017**	
Genotoxicity → **CI genotoxicity database, e.g. Kirkland et al. 2015** **e.g. OECD CoCAM**	**Non-cancer** → **Sauni et al. 2010** + Roto et al. 1980; Swennen et al. 1993; Linna et al. 2003; Verougstraete et al. 2004	

CI New Testing Program (Approval Granted in October 2023 → Studies have direct relevance for IRIS process

- In vivo genotoxicity data and oral carcinogenicity data for bioavailable Co substances, 90-day inhalation study for poorly soluble/poorly reactive Co particles

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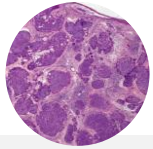
Cobalt Institute – Upcoming Data Generation For Regulatory Purposes (4 – 6 years)



Oral Carcinogenicity Study
Bioavailable Substance Group
(i.e. Co dichloride)

90-day dose-range finder
Chronic study
Carcinogenicity Study

→ Co in blood and tissues
→ Full histopathology
→ Co MOA Markers

In Vivo Genotoxicity Studies
Bioavailable Substance Group
(i.e. Co sulfate)

Transgenic Rodent Assay
COMET Assay

→ Direct genotoxic effects
→ Indirect genotoxic effects*

Sub-Chronic Inhalation Study
Poorly Soluble/ Poorly Reactive Substance Group (i.e. tricobalt tetraoxide)

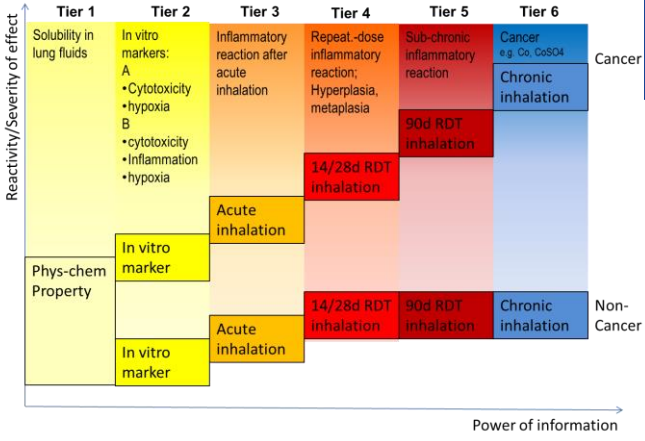
90-day repeated dose study

→ Lung burden analyses
→ Co in blood and tissues
→ Indirect genotoxic effects*

*Includes markers for: inflammation, hypoxia, oxidative stress, cytotoxicity

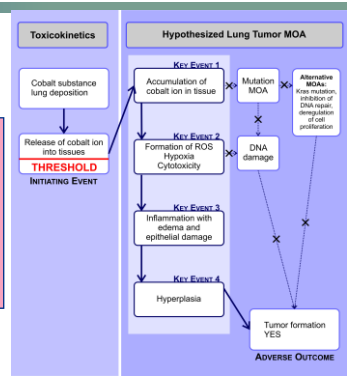
Cobalt and Cobalt Compounds: Mode-Of-Action Based Tiered Approach

Cobalt substances: Read-across approach for inhalation carcinogenicity - Concept



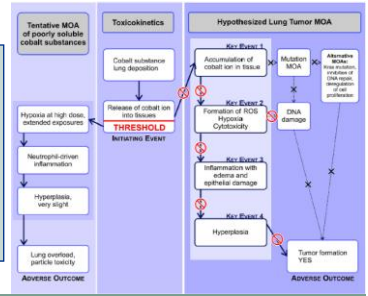
Reactive substances (e.g. Co sulfate, Co metal)

- **e.g. Co metal** → highly soluble in all <u>biologically relevant</u> fluids
- Supported by recent IARC conclusions



Poorly reactive / poorly soluble substances (e.g. tricobalt tetraoxide)

- **e.g. Tricobalt tetraoxide** → poorly soluble in all biologically relevant fluids
- Supported by recent IARC conclusions



Topic 1. Association Between Lung And Adrenal Tumor Formation

Topic 1. Association between lung and adrenal tumor formation

The IRIS program is seeking discussion on a plausible association between lung and adrenal gland tumors associated with exposure to cobalt and cobalt compounds. Background information is provided below.

An analysis of the results of NTP inhalation exposure studies in rats found an apparent association between the occurrence of pulmonary non-neoplastic lesions and the development of pheochromocytomas. This plausible association has been attributed to the adrenal response arising from systemic hypoxemia due to the reduced gas exchange induced by the lung lesions and the accompanying fibrosis and chronic inflammation. Assessment of the dependence of the tumor types impacts upon the method used to estimate composite cancer risk. A combined tumor analysis may not be appropriate if tumors do not form independently.

Upcoming Data Generation

- Oral Carcinogenicity Study
- Genotoxicity Studies

Parameters

- Systemic findings
- Co levels in blood
- Co levels in tissue – adrenal gland included

Current Database

- Co metal and Co sulfate NTP Carc. Studies: Pheochromocytomas only observed in **rats**
- Previous studies have linked these to **lung toxicity**
- Statistical analysis of 9 NTP Carc. Inhalation Studies: Concluded **overall association between lung impairment *by any cause* and elevated incidence of adrenal pheochromocytoma**
- Comparison to findings in Nickel and Nickel substance Carc. studies

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ECHA Opinion, Greim et al. 2009, Ozaki et al. 2002 – Relevance Of Pheochromocytomas

ECHA

"Pheochromocytomas are observed in numerous carcinogenicity studies and occur with relatively higher frequency in male rats, especially when the following conditions are involved: hypoxia, uncoupling oxidative phosphorylation, disturbance of the hypothalamic-endocrine axis and disturbance in calcium homeostasis with involvement of catecholamine synthesis, receptor tyrosine kinase (RET) and hypoxia-inducible factor (HIF) among others (Greim et al., 2009; Ozaki et al., 2002). Moreover, to date there is no indication that substances inducing pheochromocytomas in animal experiments also induce corresponding tumors in humans."

Greim H, Hartwig A, Reuter U, Richter-Reichhelm H-B, Thielmann H-W. (2009) Chemically induced pheochromcytomas in rats: mechanisms and relevance for human risk assessment. Crit Rev Toxicol 39, 695-718.

"When sufficiently documented and evaluated, such secondary pheochromocytomas are not relevant for classification and human risk assessment."

Ozaki K, Haseman JK, Hailey JR, Maronpot RR, Nyska A. (2002) Association of adrenal pheochromocytoma and lung pathology in inhalation studies with particulate compounds in the male F344 rat — the National Toxicology Program Experience. Toxicol. Pathol. 30, 263–270.
"Our investigation assessed the strength of these various associations and supports the possible roles of 2 chronic pulmonary lesions-fibrosis and inflammation-and hypoxemia in the induction of pheochromocytoma in the F344 male rat".

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Topic 2. Cellular Uptake and Tissue Disposition

Topic 2. Cellular Uptake and Tissue Disposition

The IRIS program is seeking discussion on cellular uptake and tissue disposition associated with exposure to cobalt and cobalt compounds. Background information is provided below.

Although cobalt bioavailability and its influence on carcinogenicity are not fully understood, it is known that cellular uptake of free cobalt ion and particles occur via different processes; differences between uptake and distribution of water-soluble and water-insoluble cobalt compounds could lead to differences in pharmacodynamics. Mechanistic information regarding cellular uptake and tissue deposition can inform dosimetric adjustments and modeling approaches.

Upcoming Data Generation

- Oral carcinogenicity study: Reactive Group
- In vivo genotoxicity studies: Reactive Group
- 90-day RDT inhalation study: Poorly Soluble Group

Parameters

- Co levels in blood and tissues
- Comet and TGR analysis in feasible tissues
- Histopathology
- Lung burden (poorly soluble particles)

Existing Database

- Danzeisen et al. 2020 – Oral Route, Reactive and Poorly Reactive Groups

Various Parameters Measured (Oral Route)

- Plasma TK
- Mass Balance
- Target Organs
- Acute and RDT effects

Question – Was Co bioavailable in Kirkland study?

- Yes, based on systemic toxicity, Danzeisen et al. 2020 and other papers in the literature

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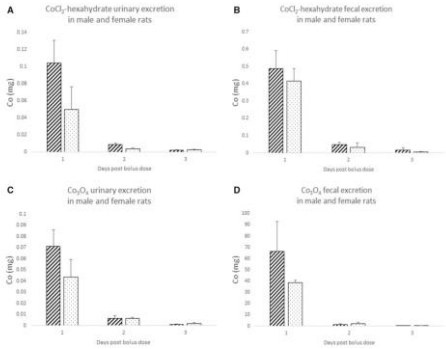
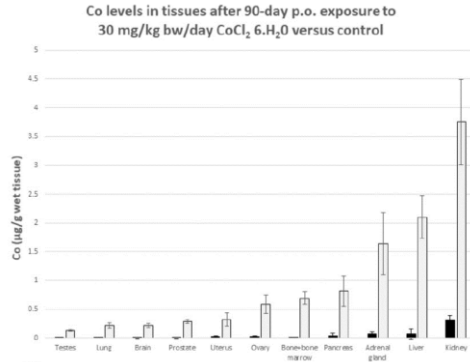
Danzeisen et al. 2020 – Cobalt Levels Mass Balance And Tissues

Mass-Balance After Acute TK (Oral)
- Co dichloride –Bioavailable
- Tricobalt tetraoxide – Poorly Bioavailable



The cobalt content from both substances appears to be excreted predominantly during the first 24-h post-gavage. The concentrations in both urine and feces decrease on day 2 by about 10-fold compared with day 1, with a further decrease on day 3 of the study.
Fecal excretion was the predominant route, with 80% (CoCl2) to 99% (Co3O4) excreted via the feces, and the remainder of the dose being excreted via urine.

Tissues After 90 Day (Oral)
- Co dichloride –Bioavailable



For most tissues and organs, the increases in Co concentration are relatively uniform, all at an elevation of around 20-fold versus control animals' tissue Co concentrations. The highest increase in tissue Co concentration versus control animals is observed in the bone marrow, where the Co concentration had multiplied by over 100-fold. The highest absolute Co concentrations following exposure were observed in the liver and kidney.

Kirkland et al. 2015 – Clastogenicity Results

Prof. Zhitkovich at EPA IRIS Co Webinar in January 2023:

- 'No clastogenic damage in bone marrow by oral Co(II) (Kirkland D, 2015) – Bioavailability?'

Kirkland et al.

- "No biologically relevant induction of MN or CA has been found in bone marrow of rodents treated with cobalt sulphate, cobalt monoxide, tricobalt tetraoxide, cobalt resinate or cobalt acetyl acetonate in the present studies. Negative results were also found with cobalt chloride (Gudi and Ritter, 1998), cobalt 2-ethyl hexanoate (Richold et al., 1981) and cobalt metal (NTP, 2013)."

Danzeisen et al. 2020 – Acute TK Results

Table 4. Pharmacokinetic Parameters for Several Cobalt Compounds

Pharmacokinetic Parameters of Cobalt Dichloride Hexahydrate, Tricobalt Tetraoxide, Cobalt Sulfide, and Cobalt Lithium Dioxide in Rats (Noncompartmental Analysis)[a]

Test item	Dose level [mg test item/kg]	Dose level [mg Co/kg]	Sex	C_{max}[b] [µg/l]	$t_{1/2}$ [h]	K_{el} [1/h]	$AUC_{0-t\,last}$/cobalt dose [(h·µg/l)/(mg/kg)]	Bioavailability [%]
$CoCl_2.6H_2O$	0.1 (IV)	0.0248	M	1.05	88.2	0.0079	293.6	Defined as 100
			F	0.40	40.7	0.0170	117.3	Defined as 100
$CoCl_2.6H_2O$	10 (PO)	2.48	M	2.51	14.2	0.0489	20.0	6.81 (absolute)
			F	2.61	13.7	0.0508	13.7	11.7 (absolute)
Co_3O_4	300 (PO)	214	M	2.08	17.3	0.0402	0.18	0.06 (relative)
			F	1.10	16.1	0.0430	0.12	0.1 (relative)
$CoCl_2.6H_2O$	0.1 (IV)	0.0248	M	0.42	13.9	0.0499	124.7	Defined as 100
			F	0.42	10.1	0.0686	114.7	Defined as 100
CoS	300 (PO)	196	M	2.01	16.8	0.0413	0.10	0.08 (relative)
			F	2.01	14.9	0.0464	0.10	0.09 (relative)
$CoLiO_2$	300 (PO)	180	M	3.45	13.0	0.0535	0.37	0.30 (relative)
			F	2.88	12.20	0.0568	0.29	0.25 (relative)

[a]The values presented in this table are rounded for reasons of better readability.
[b]Values obtained from plasma analysis (data provided by Fraunhofer-IME), all other values calculated by pharmacokinetic evaluation performed by LPT.
Abbreviations: M, male; F, female; IV, intravenous; PO, per os.

Co dichloride was bioavailable in Kirkland et al. 2015 in vivo bone marrow CA study.

Danzeisen et al. 2020

- Co dichloride bioavailability after acute bolus dose was 7 and 12% in males and females, respectively

Kirkland et al. 2015

- Clear signs of systemic toxicity (i.e. mortality before end of 5 day exposure period)
- In vivo CA studies achieved target organ exposures to the soluble substances

Nation et al. 1983

- Demonstrated that cobalt chloride administered orally to rats achieved significant exposure levels in multiple tissues.

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Topic 3. Cobalt Particle Toxicity

Topic 3. Cobalt Particle Toxicity

The IRIS program is seeking discussion on particle toxicity associated with exposure to cobalt and cobalt compounds. Background information is provided below.

In addition to potential differences in particle ion uptake and distribution that might influence tissue dosimetry, cobalt is a redox-active transition metal. Cobalt particles may have a greater effect than ions in catalyzing production of reactive oxygen species (ROS). How cobalt ions are released in vivo also differs between water-soluble and water-insoluble cobalt compounds. Updating the mechanistic evidence concerning whether cobalt particles may elicit direct toxicity contributing to carcinogenesis will help inform the choice of the particle lung dose metric used for rodent-to-human extrapolation and dose-response.

Upcoming Data Generation

- 90-day RDT inhalation study – For poorly reactive / poorly soluble group

Existing database

- Inhalation read-across approach: ToxTracker (**Derr** et al. 2022)
- Inhalation read-across approach: In vivo 14-day and 28-day RDT data for tricobalt tetraoxide (poorly soluble particle) (**Burzlaff** et al. 2022)
- Previous studies and papers by **Lison** Group

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Topic 4. Proposed MOA Of Cobalt Carcinogenicity

Topic 4. Proposed MOA of cobalt carcinogenicity

The IRIS program is seeking discussion on the potential MOA of cobalt and cobalt compounds. Background information is provided below.

There is evidence that cobalt-induced neoplastic development likely involves pathways of genotoxicity, oxidative stress (and generation/scavenging of ROS), and stabilization of hypoxia-inducible factor 1α. Other evidence suggests that cobalt genotoxicity involves primarily clastogenic effects, as well as direct and indirect DNA damage and inhibition of DNA repair. Updating the current evidence in the proposed cobalt cancer MOA, including capturing any new evidence of mechanistic responses beyond those previously described, will help inform the dose-response analyses, pharmacokinetic evaluations, and animal-to-human extrapolation methodologies.

Substances that can release cobalt ions in vivo, both water soluble and insoluble, likely define the domain of applicability for this assessment.

Upcoming Data Generation

- Oral carcinogenicity: Bioavailable group
- In vivo genotoxicity studies: Reactive Co substances
- 90-day RDT inhalation study: Poorly reactive Co substances

Parameters

- Oxidative stress
- Hypoxia
- Cytotoxicity
- Inflammation
- Genotoxicity
- Lung Burden

Present database

- Inhalation read-across approach for reactive and poorly reactive / poorly soluble groups
- Solubility in artificial biological fluids
- In vitro cellular markers – Hypoxia, cytotoxicity
- ToxTracker Assay – Hypoxia, cytotoxicity, genotoxicity, oxidative stress
- In vivo acute, 14d, 28d data – Hypoxia, cytotoxicity, oxidative stress, inflammation
- Kirkland 2015 – Genotoxicity data

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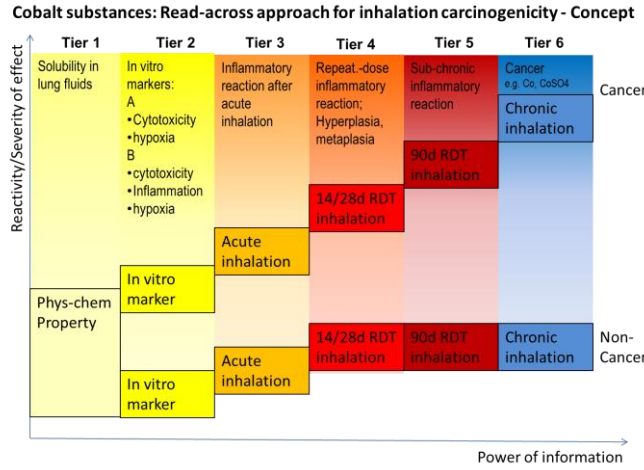
Cobalt And Cobalt Compounds: Grouping



Reactive Group: Testing On-Going
Co sulfate
Co dichloride
Co diacetate
Co dinitrate
Co carbonate
Co metal
Co monoxide
Co dihydroxide

Poorly Reactive / Poorly Soluble Group: Testing On-Going
Tricobalt tetraoxide
Co sulfide
Co hydroxide oxide
Co lithium dioxide

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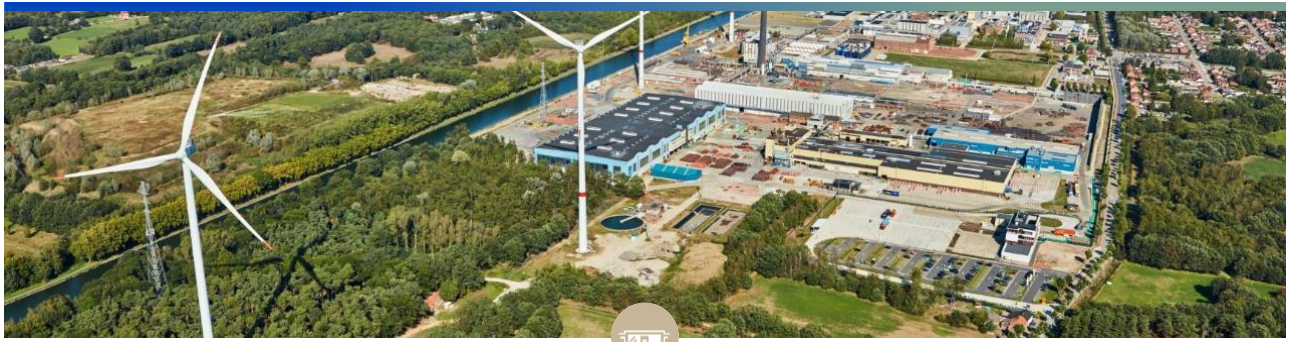


4 – Epidemiology Data and Comparisons of Potency

Assessment of epidemiologic literature

Is the cobalt PPRTV proposed by EPA consistent with worker cohort analyses reported in Marsh et al. 2017?

- Sensitivity analysis to evaluate the concordance of the epidemiology and animal-based IURs
- Objective to provide a bounding estimate on cancer potency based on human data
- Findings suggest animal-based IURs may overestimate the human experience based on worker data

Marsh et al. 2017

Total sample size and Co exposure of the study population

- Sample size: 22,121 workers
- Average Intensity of Exposure (AIE)
  - Median: 0.006 mg/m^3
  - Standard deviation (SD): = 0.029 mg/m^3

All excess cancer and SMR calculations were based on the highest cobalt exposure group in Marsh et al. 2017

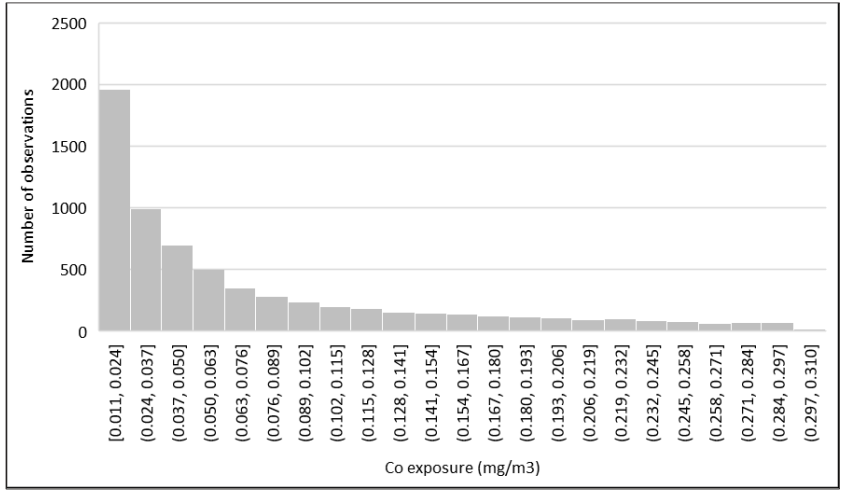
- AIE: 0.011-0.300 mg/m^3
- SMR (95% CI): 1.15 (0.92-1.43)

Population and exposure estimates

A Monte Carlo simulation was performed to estimate population size and distribution of Co exposure of the highest exposure group:

- Generated 22,121 random AIE values from a lognormal distribution with location parameter = median, scale parameter = SD, and threshold parameter = 0
- Resulted in 6,736 observations with an exposure of at least 0.011 mg/m^3
- The median, 2.5%-tile, and 97.5%-tile were calculated from these 6,736 random values

Distribution of Co exposure in highest exposure group



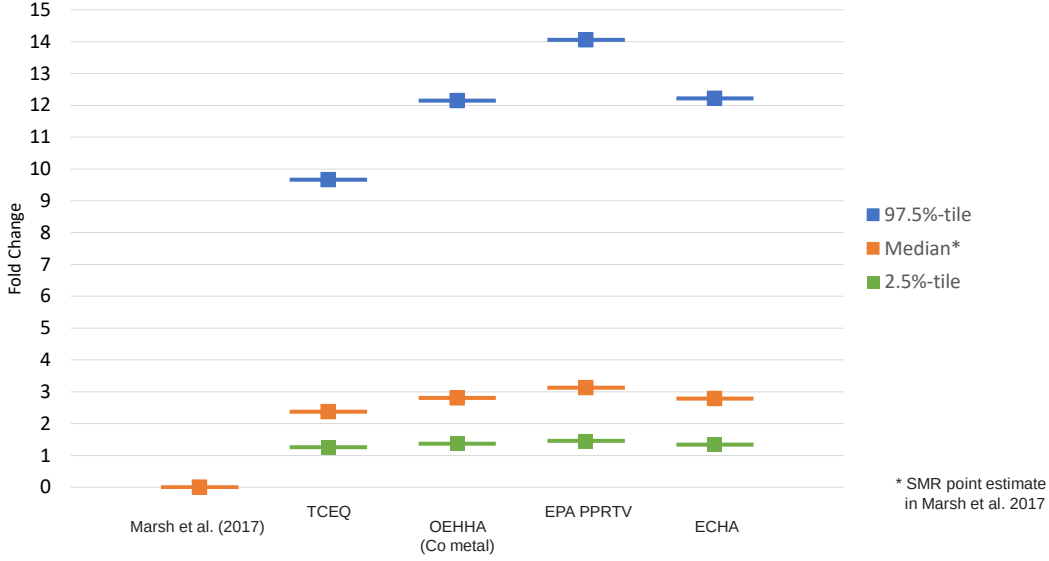
Using PPRTV*

	AIE (highest exposure group; mg/m^3)	Respirable Fraction (mg/m^3)	Lifetime Risk	Excess Cancer Count	SMR
Min	0.011	0.006	0.007	45.41	1.64
2.5%-tile	0.012	0.006	0.007	48.25	1.68
Median	0.045	0.022	0.028	185.31	3.60**
97.5%-tile	0.262	0.131	0.161	1,081.24	16.16
Max	0.300	0.150	0.184	1,236.84	18.35

* All worker exposure estimates were converted to appropriate population equivalent

** > 3 x higher than observed in Marsh et al. 2017

Rs calculated with various potency values compared Marsh et al. (2017) SMR



For further information, please contact:
Vanessa Viegas, Principal Toxicologist (Human Health)
vviegas@cobaltinstitute.org

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Burzlaff et al. (2022). "A tiered approach to investigate the inhalation toxicity of cobalt substances. Tier 4: Effects from a 28-day inhalation toxicity study with tricobalt tetraoxide in rats." Regul Toxicol Pharmacol. https://doi.org/10.1016/j.yrtph.2022.105129

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