

Quantitative Risk Assessment of the Genotoxicity and Tumorigenicity of CoCr- Containing Hip Implants

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Declaration of interest

I am employed by Cardno ChemRisk, a consulting firm that provides scientific advice to the government, corporations, law firms, and various scientific/professional organizations.

Cardno ChemRisk has been engaged by DePuy Orthopaedics, Inc., a manufacturer of prosthetic devices, some of which contain cobalt and chromium, to provide general consulting and expert advice on scientific matters as well as litigation support. The research that will be presented was conducted and prepared exclusively by Cardno ChemRisk employees without review or comment by DePuy employees or counsel.

It is likely that this work will be relied upon in medical research, nutrition research, and litigation. It is possible that any or all of the authors of this research may be called upon to serve as expert witnesses. Funding for the preparation of this research was primarily provided by DePuy.

Outline

- *A brief* history of hip implants

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- *A brief history of hip implants*
- Applying the risk assessment paradigm to evaluate the safety of CoCr-containing hip implants
 - e.g., assessing the risk of systemic health effects from Co exposure

Outline

Aside from epidemiology studies, can informed conclusions be reached regarding potential cancer risks in CoCr MoM implant patients using fundamental toxicology and exposure assessment methods?

- The TBCC study: ***T**oxicology-**b**ased **c**ancer **c**ausation analysis of CoCr-containing hip implants: A quantitative assessment of genotoxicity and tumorigenicity studies. *J Appl Tox.* 34(9): 939-967.”
 - General overview
 - From math to conclusions*

Outline

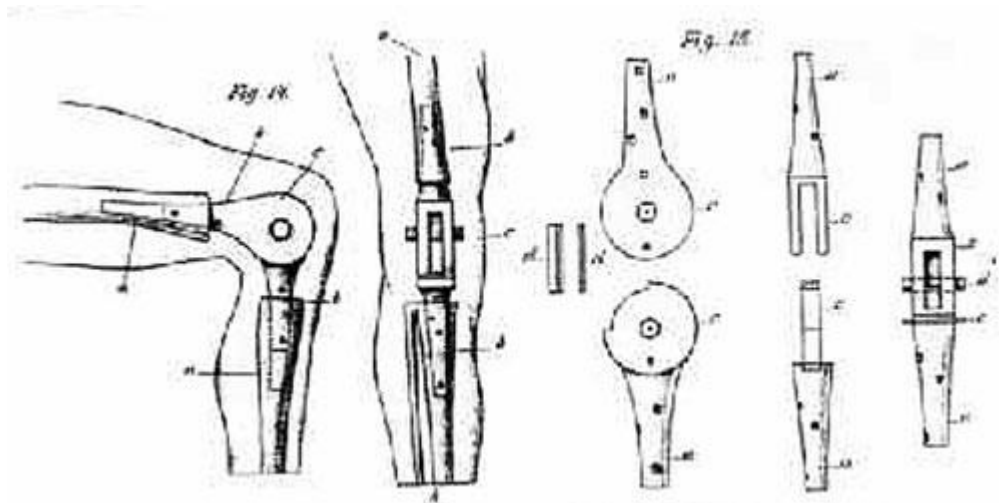
- A *brief* history of hip implants
- Applying the risk assessment paradigm to evaluate the safety of CoCr-containing hip implants
- The TBCC study: “*Toxicology-based cancer causation analysis of CoCr-containing hip implants: A quantitative assessment of genotoxicity and tumorigenicity studies. J Appl Tox. 34(9): 939-967.*”
- Limitations and closing comments

A brief history of hip implants

Themistocles Glück invented the first hip implant

Background

- Long history of use
 - Dates back to 1891
 - Themistocles Glück
- Designed and implanted artificial wrists, elbows, shoulders, hips, knees, and ankles



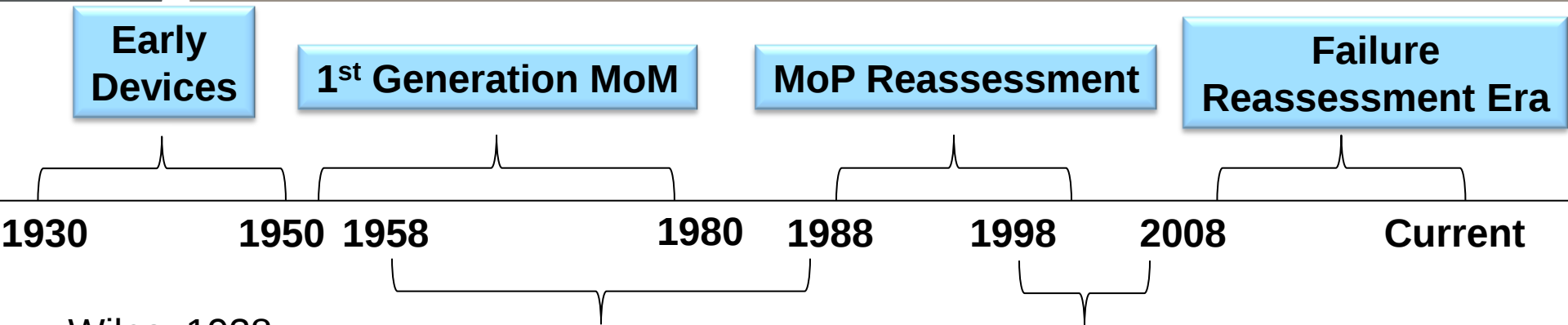
Hip implants are used to treat several medical conditions

Background

- Long history of use
 - Dates back to 1891
 - Themistocles Glück
- Medical benefits
 - Improve the quality of life and reduce pain from:
 - Osteoarthritis
 - Rheumatoid arthritis
 - Osteonecrosis (*avascular necrosis*)
 - Injury of the hip joint
 - Bone tumors that break down the hip joint
 - Developmental dysplasia



Evolution of MoM hip implants



Wiles, 1938



Charnley MoP



McKee-Farrar, 1956

2nd Generation MoM/MoP



DePuy, 2003

Concerns arise regarding the safety of MoM hip implants

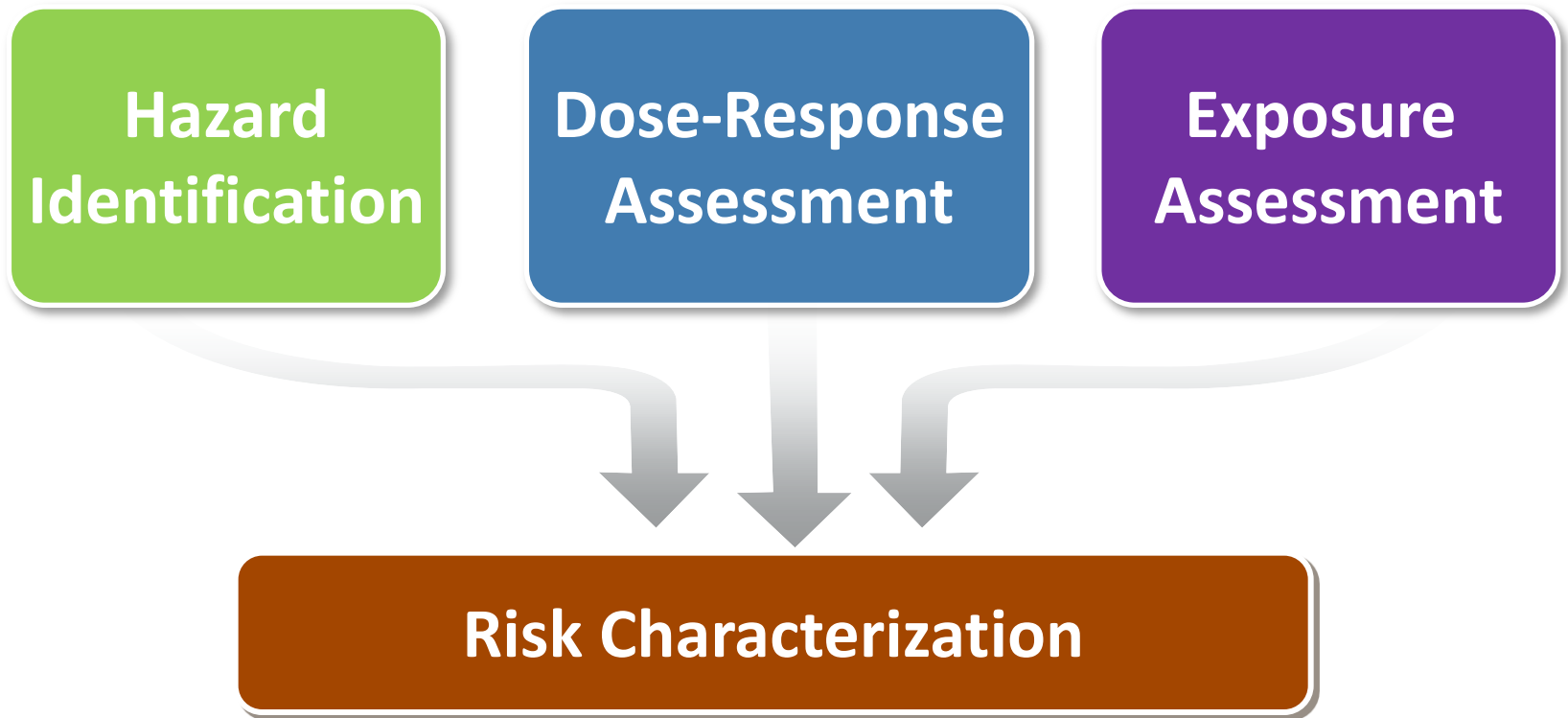
Background

- Long history of use
 - Dates back to 1891
- Medical benefits
 - Reduce pain and improve the quality of life
- ***Recently, higher than acceptable revision rates have been reported for some MoM hip prostheses***
 - Concerns raised about the safety of these devices

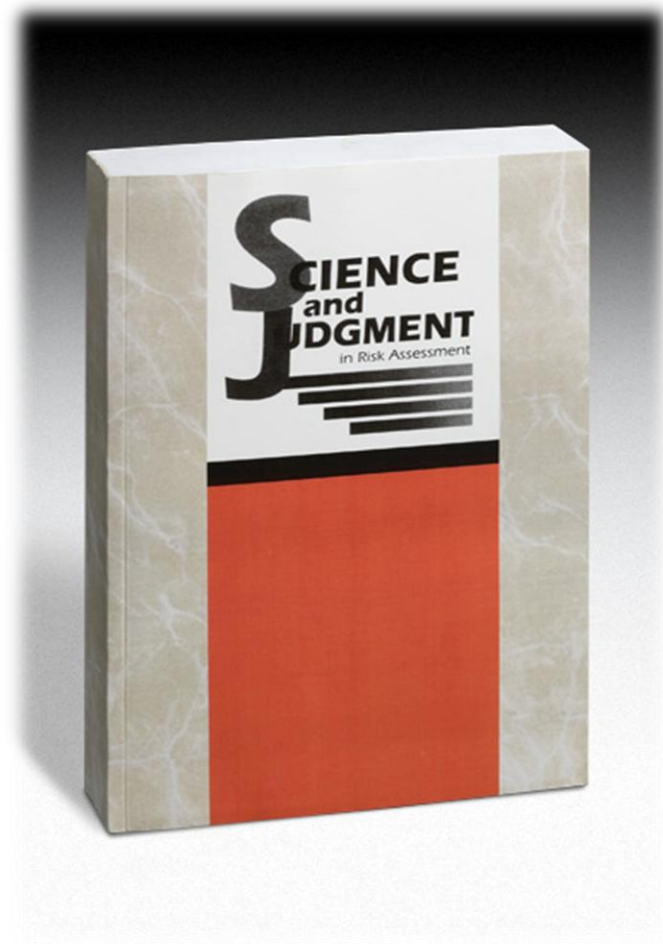
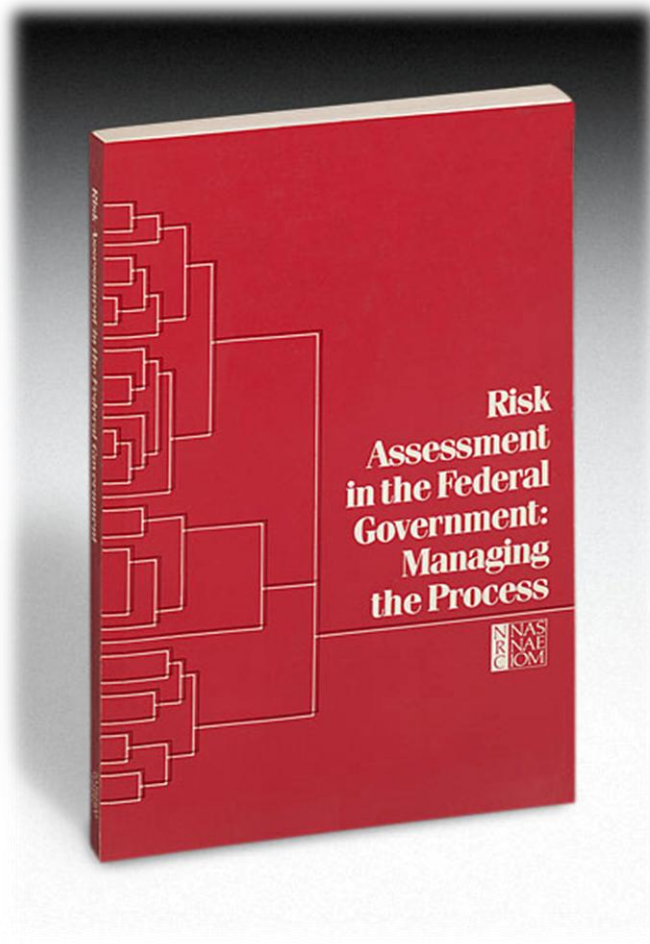


Applying the risk assessment
paradigm to evaluate the safety of
CoCr-containing hip implants

The four steps of risk assessment



National Research Council guidelines for risk assessment



Federal regulatory agencies that rely on risk assessment

➤ **FDA**



U.S. Food and Drug Administration
Protecting and Promoting *Your Health*

➤ **EPA**



United States Environmental Protection Agency

➤ **CPSC**



**UNITED STATES
CONSUMER PRODUCT SAFETY COMMISSION**

Concerns regarding elevated blood Co concentrations in MoM patients

Dose-response data gap

- Concerns were raised regarding blood Co concentrations
 - All MoM hip implant patients have elevated blood Co concentrations
 - Most levels <10 µg/L
- The relationship between blood Co concentrations (dose) and systemic health effects (response) was undefined

Risk assessment of systemic health effects from Co exposure

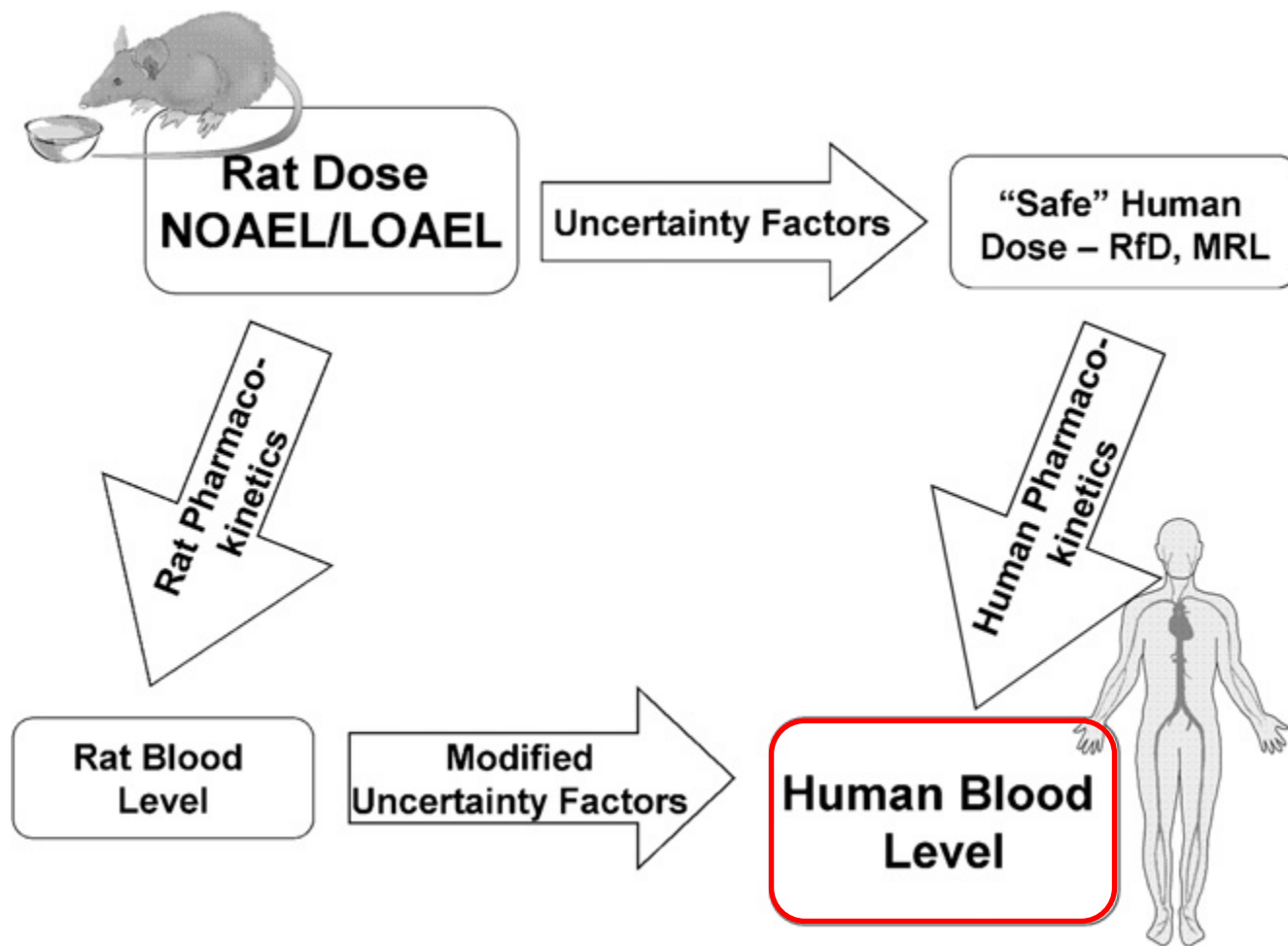
DOSE-RESPONSE RELATIONSHIPS FOR BLOOD COBALT CONCENTRATIONS AND HEALTH EFFECTS: A REVIEW OF THE LITERATURE AND APPLICATION OF A BIOKINETIC MODEL

Brent L. Finley, Andrew D. Monnot, Shannon H. Gaffney, Dennis J. Paustenbach

ChemRisk, LLC, San Francisco, California, USA

Cobalt (Co) is an essential component of vitamin B₁₂. As with all metals, at sufficiently high doses, Co may exert detrimental effects on different organ systems, and adverse responses have been observed in animals, patients undergoing Co therapy, and workers exposed to respirable Co particulates. Although blood Co concentrations are postulated to be the most accurate indicator of ongoing Co exposure, little is known regarding the dose-response relationships between blood Co concentrations and adverse health effects in various organ systems. In this analysis, the animal toxicology and epidemiology literature were evaluated to identify blood Co concentrations at which effects have, and have not, been reported. Where necessary, a biokinetic model was used to convert oral doses to blood Co concentrations. **Our results indicated that blood Co concentrations of 300 µg/L and less have not been associated with adverse responses of any type in humans.** Concentrations of 300 µg/L and higher were associated with certain hematological and reversible endocrine responses, including polycythemia and reduced iodide uptake. Blood Co concentrations of 700–800 µg Co/L and higher may pose a risk of more serious neurological, reproductive, or cardiac effects. These blood concentrations should be useful to clinicians and toxicologists who are attempting to interpret blood Co concentrations in exposed individuals.

The use of biokinetic or PBPK models has been key to our risk assessments



Recent studies agree with the conclusions from our Co dose-response analysis

Systemic toxicity related to metal hip prostheses

S. M. BRADBERRY,¹ J. M. WILKINSON,² and R. E. FERNER³

¹*West Midlands Poisons Unit, City Hospital, Birmingham, UK*

²*Department of Human Metabolism, University of Sheffield, Sheffield, UK*

³*West Midlands Centre for Adverse Drug Reactions, City Hospital, Birmingham, UK*

“We consider that in 10 patients the systemic features were likely to be associated with cobalt exposure; all cases had a peak blood cobalt concentration over 250 µg/L”

What about the risk of cancer in MoM patients?

Concerns over cancer risk in young recipients

- MoMs are being implanted in an increasingly younger patient population
 - These individuals will live longer than the typical implant residency of 10 years
- The latency of cancer is typically ~20 years
 - The potential cancer risk associated with *long-term exposures* to the metallic debris generated by these devices is largely unknown

Epidemiology of cancer in hip implant patients

- Epidemiology studies on hip implant cohorts have been conducted, but several shortcomings exist:
 - Insufficient latency periods
 - Few studies on U.S. cohorts
 - No studies specifically of CoCr MoM patients
- The current epidemiological weight-of-evidence does not indicate a cancer risk related to CoCr MoM implants, however questions remain regarding the completeness of these studies

The question at hand

Aside from epidemiology studies, can informed conclusions be reached regarding potential cancer risks in CoCr MoM implant patients using fundamental toxicology and exposure assessment methods?

Our approach to addressing the question at hand

Aside from epidemiology studies, can informed conclusions be reached regarding potential cancer risks in CoCr MoM implant patients using fundamental toxicology and exposure assessment methods?

➤ Approach:

Quantitative cancer causation analysis for CoCr MoM implants using toxicology and exposure assessment principles and methodologies

- Can predict whether a given compound may pose a substantial cancer risk to humans under a variety of plausible exposure conditions
- Can be helpful in situations where cancer epidemiology data are either unavailable or incomplete

TBCC overview



Hazard Identification

Identified all *in vitro* studies with human cell lines and animal bioassays that utilized Co and Cr(III) ions or particulates as test articles with genotoxic and/or tumorigenic endpoints.



Dose Response

Converted test article doses from experiments into common metrics, and determined NOAELs and LOAELs associated with the endpoints of interest. Devised a weighting scheme to rank endpoints by their significance for evidence of carcinogenicity.

TBCC overview



Exposure Assessment

Reported blood metal concentrations and wear rates in patients with well functioning hip implants from *Sidaginamale et al., 2013* were utilized to estimate body burdens of Co and Cr(III) ions and particulates.



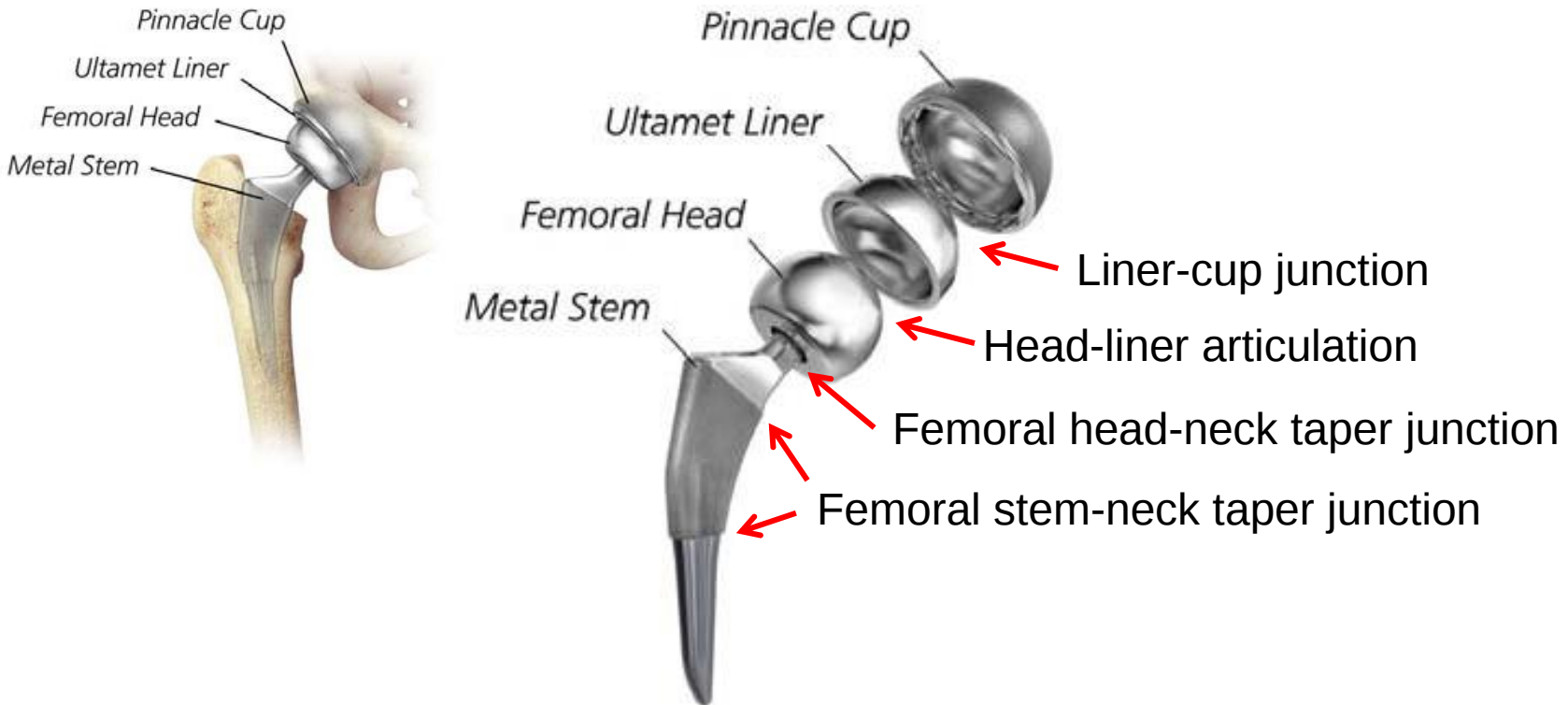
Risk Characterization

Divided experimental NOAELs and LOAELs by patient exposures to derive exposure quotients. The greater the value of the exposure quotient, the lower the likelihood of genotoxicity or carcinogenicity occurring as a result of exposure to hip implant wear debris.

The TBCC study

Defining the test articles – wear debris

Hazard identification



- Corrosion, fretting wear, articulation, and dissolution generate:
 - Co(II) and Cr(III) ions
 - Co/Cr nanoparticles (10-120 nm)

IARC classification of Co, Cr, and CoCr implant alloys

Hazard identification

- Co metal, Co sulfate, and Co(II) salts
 - Group 2B - *possibly carcinogenic to humans*

- Cr metal and Cr(III) compounds
 - Group 3 - *not classifiable as to their carcinogenicity to humans due to inadequate information*

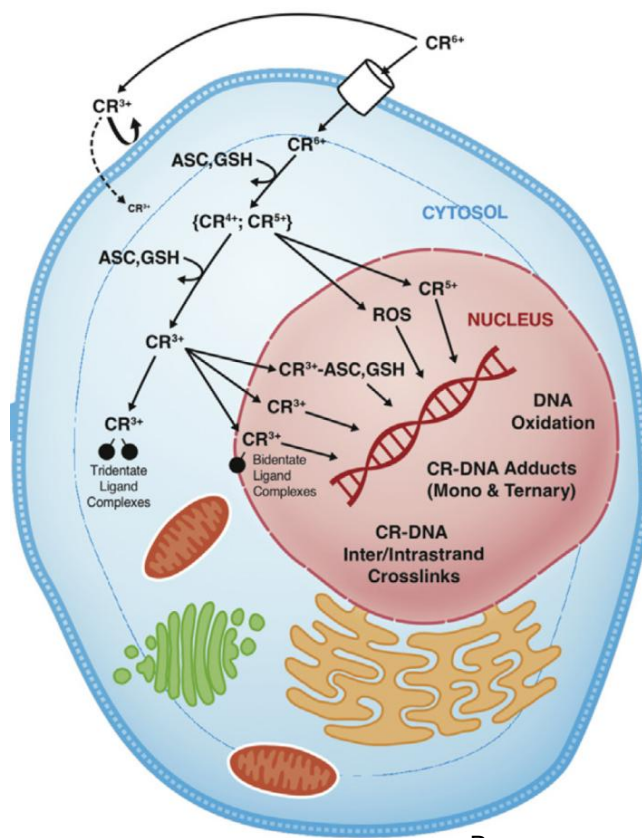
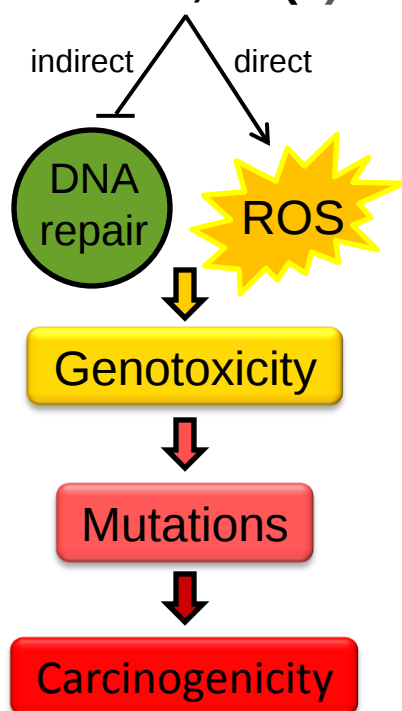
- CoCr implant alloys
 - Group 3

Co and Cr can be carcinogens

Hazard identification

- At high doses, metals can be genotoxic due to their general reactivity
- *Octet and dodecet rules* – metals react to complete the electron occupancy of their outermost valence shell and, in turn, acquire stability

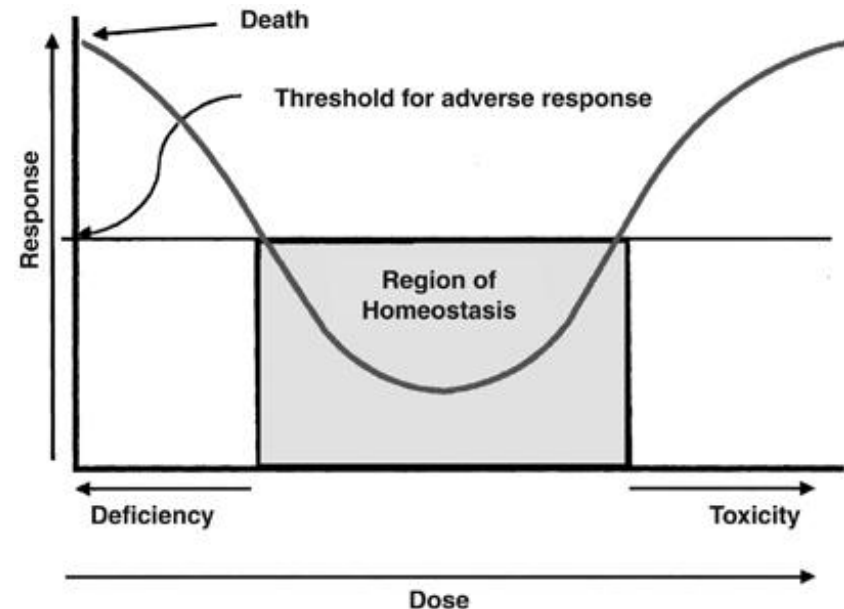
Co metal, Co(II)



Co and Cr are threshold carcinogens

Hazard identification

- Bioavailability of Co and Cr(III) is limited
 - Precipitate as oxides, hydroxides, and phosphates
 - Sequestered by intracellular ligands
 - Ascorbic acid, GSH, cysteine, and sulfhydryl containing proteins
- Co and Cr(III) are essential elements
 - Co
 - Vitamin B₁₂
 - Cr(III)
 - GTF
 - LMWCr
 - phosphoglucomutase



Defining dose metrics – values reported in MoM patients

Dose-response assessment

- Three dose metrics are routinely seen in the literature
 - $\mu\text{g/L}$ – metal ion blood concentrations
 - $\mu\text{g/g}$ – tissue burdens of metal particulate
 - mm^3/yr – implant wear rates

- ~80 studies identified in the literature were sorted into **four categories** based on dose metrics
 - 1) $\mu\text{g/L}$ – *in vitro* assays with soluble ions
 - 2) $\mu\text{g/g}$ – *in vitro* assays with particulates
 - 3) $\mu\text{g/L}$ – *in vivo* assays with soluble ions
 - 4) mg/kg-day (mm^3/yr) – *in vivo* assays with particulates

Conversion of experimental doses into common metrics (1)

Dose-response assessment

- **Category 1** – *in vitro* assays with Co/Cr soluble ions
- Converting doses in μM into $\mu\text{g/L}$

$$\begin{array}{ccccc} \text{ion concentration} & & \text{Co/Cr gram atomic mass} & & \\ \frac{x \mu\text{mol}}{1} & \times & \frac{59/52 \mu\text{g}}{\mu\text{mol}} & = & \frac{x \mu\text{g}}{1} \end{array}$$

Conversion of experimental doses into common metrics (2)

Dose-response assessment

- **Category 2 – *in vitro* assays with Co/Cr particulates**
 - Converting doses in $\mu\text{g/L}$, mg/cm^2 , and $\mu\text{m}^3/\text{cell}$ into $\mu\text{g/g}$

particle dose		unit conversion		given assay conditions		cell weight	
$\frac{x \mu\text{g}}{\text{l}}$	$\times$	$\frac{1}{1000 \text{ ml}}$	$\times$	$\frac{\text{ml}}{10^x \text{ cells}}$	$\times$	$\frac{\text{cell}}{2.7 \times 10^{-11} \text{ g}}$	$= \frac{x \mu\text{g}}{\text{g}}$

particle dose		unit conversion		given assay conditions		cell weight	
$\frac{x \text{ mg}}{\text{cm}^2}$	$\times$	$\frac{1000 \mu\text{g}}{\text{mg}}$	$\times$	$\frac{x \text{ cm}^2 \text{ dish}}{10^x \text{ cells}}$	$\times$	$\frac{\text{cell}}{2.7 \times 10^{-11} \text{ g}}$	$= \frac{x \mu\text{g}}{\text{g}}$

particle dose		unit conversion		particle density		unit conversion		cell weight	
$\frac{x \mu\text{m}^3}{\text{cell}}$	$\times$	$\frac{10^{-12} \text{ ml}}{\mu\text{m}^3}$	$\times$	$\frac{8.3 \text{ g}}{\text{ml}}$	$\times$	$\frac{10^6 \mu\text{g}}{\text{g}}$	$\times$	$\frac{\text{cell}}{2.7 \times 10^{-11} \text{ g}}$	$= \frac{x \mu\text{g}}{\text{g}}$

Conversion of experimental doses into common metrics (3)

Dose-response assessment

➤ Category 3 – *in vivo* assays with Co/Cr soluble ions

➤ Converting doses in mg/kg-day into µg/L

➤ Calculate mg/kg-day Co/Cr doses

- Study information
- Molar masses

➤ Dosimetric adjustment factor (DAFs)

- Convert animal doses into human equivalent doses (HEDs)
- DAFs: rat – 4.16, mouse – 7.18, hamster – 5.26 and pig – 1.04

$$\frac{\text{animal dose}}{\text{DAF}} = \text{HED}$$

➤ HEDs → Co/Cr PBPK models

- Human Co/Cr blood levels (µg/L)

Conversion of experimental doses into common metrics (4)

Dose-response assessment

➤ Category 4 – *in vivo* assays with Co/Cr particulates

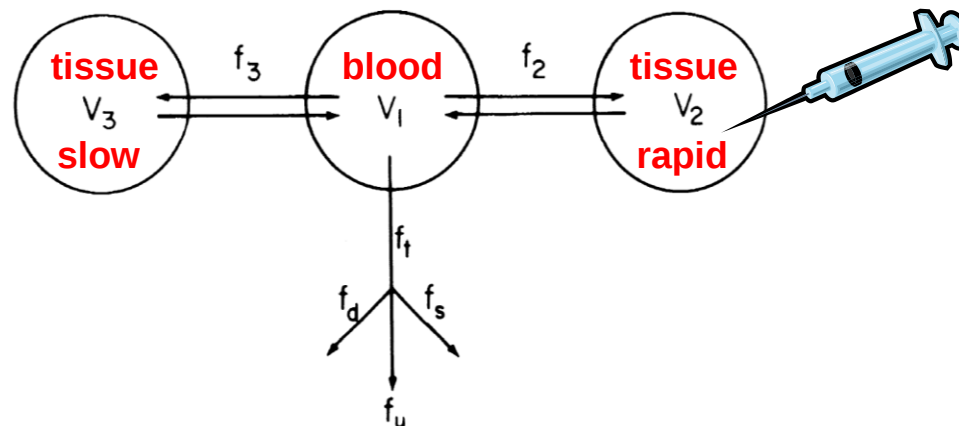
➤ Determining doses in mg/kg-day

➤ Calculate mg/kg-day Co/Cr doses

- Study information
- Molar masses

➤ Determine LADDs

- Model single bolus injections of Co/Cr particulate
- Continuous dose rates = particle dissolution rates



Weighting paradigm for the endpoints of interest

Dose-response assessment

Significance	Marker	Experiment
high	tumor formation	<i>in vivo</i>
medium	micronuclei formation chromosomal aberrations	
low	SSBs, DSBs oxidative DNA damage DNA repair	<i>in vitro</i>

Establishing Co and Cr(III) blood concentrations under normal wear conditions

Exposure assessment

➤ Category 1 & 3 – *in vitro* & *in vivo* assays with soluble ions

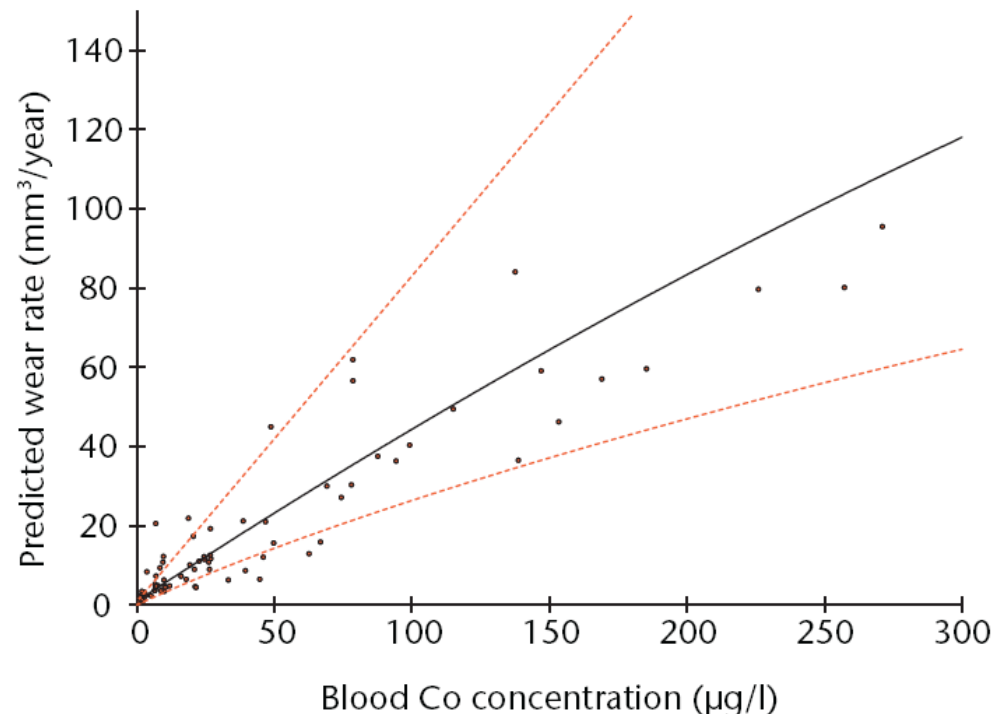
➤ Co and Cr(III) blood levels associated with 1 mm³/yr wear rate

➤ *Sidaginamale et al., 2013*

➤ Blood samples from 3,042 patients

➤ ~2 µg/L Co

➤ ~5 µg/L Cr(III)



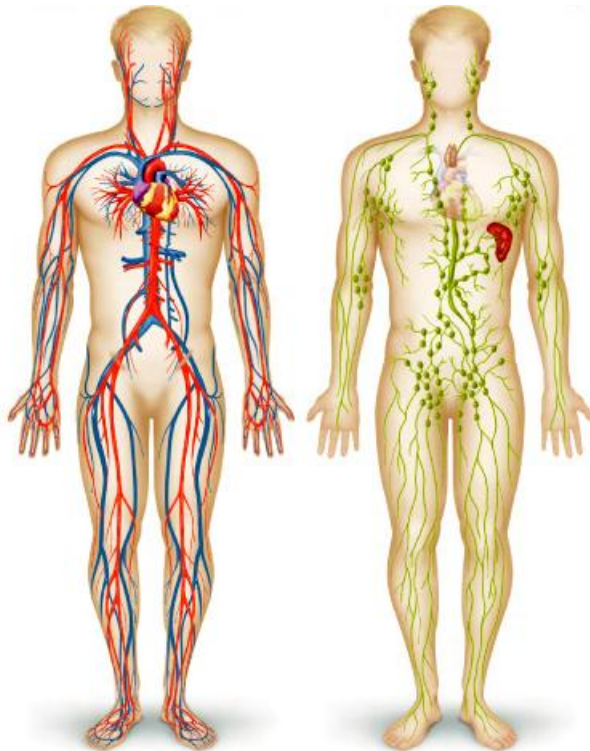
Establishing tissue burdens of CoCr, Co, and Cr(III) particulate under normal wear (1)

Exposure assessment

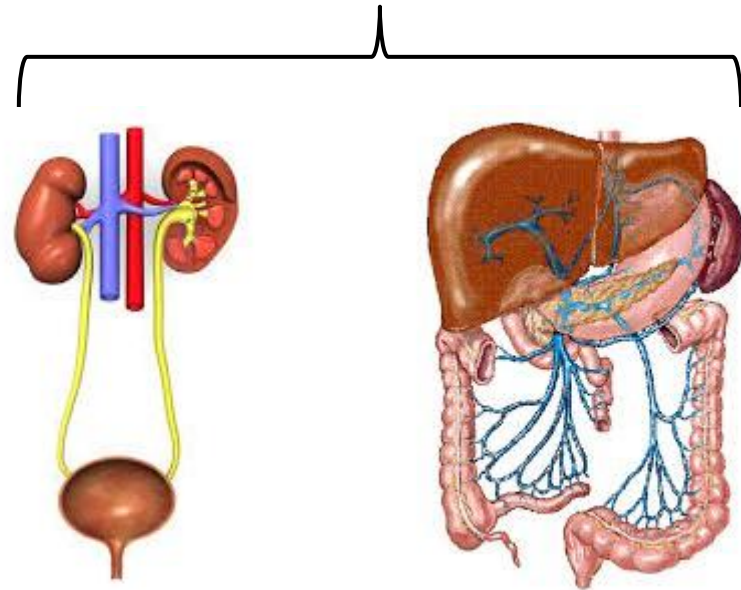
➤ Category 2 – *in vitro* assays with Co/Cr particulates

➤ Defining tissues of interest

circulatory & lymphatic
systems



metabolism & excretion
systems



Establishing tissue burdens of CoCr, Co, and Cr(III) particulate under normal wear (2)

Exposure assessment

➤ Category 2 – *in vitro* assays with Co/Cr particulates

➤ Estimating dry tissue weight

➤ Reference Man (*ICRP, 1992*)

$$\text{➤ } \frac{40 \text{ kg H}_2\text{O}}{70 \text{ kg bw}} = 57\%$$

Organ	Wet Weight (kg) ^a	Relative Weight (%) ^b
Aorta	0.1	0.14
Blood vessels	0.2	0.29
Erythrocytes (total)	2.4	3.40
Gall bladder	0.01	0.01
Heart	0.33	0.47
Intestine (small & large)	1.1	1.57
Kidneys (2)	0.31	0.44
Liver	1.8	2.60
Lymphocytes (total)	1.5	2.10
Lymphatic tissue	0.5*	0.71
Lymph nodes	0.25	0.36
Spleen	0.18	0.26
Thymus	0.02	0.029
Ureters (2)	0.016	0.023
Urethra	0.01	0.014
Urinary bladder	0.045	0.064
Total weight	8.77	
Water weight (57% of total)	5.00	
Total dry weight (kg)	3.77	

^aValues obtained from Reference Man (*ICRP, 1992*).

^bRelative to an adult weight of 70 kg (*ICRP, 1992*).

*Weight after deducting contribution of resident lymphocytes.

Establishing tissue burdens of CoCr, Co, and Cr(III) particulate under normal wear (3)

Exposure assessment

➤ Category 2 – *in vitro* assays with Co/Cr particulates

➤ Deriving particulate tissue burdens

➤ MoM hip implant CoCr alloys

➤ ~64% Co

➤ ~28% Cr

wear rate	unit conversion	alloy density	unit conversion	implant residence	tissue dry weight	unit conversion	CoCr tissue concentration
$\frac{1 \text{ mm}^3}{\text{year}}$	$\times \frac{0.001 \text{ ml}}{\text{mm}^3}$	$\times \frac{8.3 \text{ g}}{\text{ml}}$	$\times \frac{10^6 \mu\text{g}}{\text{g}}$	$\times 10 \text{ years}$	$\times \frac{1}{3.77 \text{ kg}}$	$\times \frac{1 \text{ kg}}{1000 \text{ g}}$	$= \frac{22 \mu\text{g}}{\text{g}}$

CoCr tissue concentration

$$\frac{22 \mu\text{g}}{\text{g}}$$

Co/Cr percent composition

$$\times 0.64/0.28$$

$=$

Co/Cr tissue concentration

$$\frac{14 \mu\text{g Co}/6.2 \mu\text{g Cr}}{\text{g}}$$

Establishing mg/kg-day doses of CoCr, Co, and Cr(III) particulate under normal wear

Exposure assessment

➤ Category 4 – *in vivo* assays with Co/Cr particulates

➤ Deriving mg/kg-day particulate doses

wear rate		unit conversion		unit conversion		alloy density		unit conversion		default human weight		CoCr prosthetic dose equivalent
$\frac{1 \text{ mm}^3}{\text{year}}$	×	$\frac{\text{year}}{365 \text{ days}}$	×	$\frac{0.001 \text{ ml}}{\text{mm}^3}$	×	$\frac{8.3 \text{ g}}{\text{ml}}$	×	$\frac{1000 \text{ mg}}{\text{g}}$	×	$\frac{1}{70 \text{ kg}}$	=	$\frac{0.00032 \text{ mg}}{\text{kg per day}}$

prosthetic dose equivalent		Co/Cr percent composition		Co/Cr dose equivalent
$\frac{0.00032 \text{ mg}}{\text{kg per day}}$	×	0.64/0.28	=	$\frac{0.00021 \text{ mg Co}/0.000091 \text{ mg Cr}}{\text{kg per day}}$

Review

Study category	Assay type	Co/Cr form	NOAEL/LOAEL dose metric	Metallic species	Estimated body burdens
1	<i>in vitro</i>	soluble	$\mu\text{g/L}$	Co	2
				Cr	5
				CoCr	22
2	<i>in vitro</i>	particulate	$\mu\text{g/g}$	Co	14
				Cr	6.2
				CoCr	0.00032
3	<i>in vivo</i>	soluble	$\mu\text{g/L}$	Co	2
				Cr	5
				CoCr	0.00021
4	<i>in vivo</i>	particulate	mg/kg-day	Co	0.00021
				Cr	0.000091
				CoCr	0.000091

Assessing the potential genotoxic or carcinogenic health risk – exposure quotient

Risk characterization

➤ Similar to MOS or MOE

➤
$$\frac{\text{NOAEL}}{\text{exposure}}$$

➤ Exposure quotient (EQ)

➤
$$\frac{\text{NOAEL/LOAEL}}{\text{estimated body burden}}$$

Study category	Metallic species	Estimated body burdens
1	Co	2
	Cr	5
2	CoCr	22
	Co	14
	Cr	6.2
3	Co	2
	Cr	5
4	CoCr	0.00032
	Co	0.00021
	Cr	0.000091

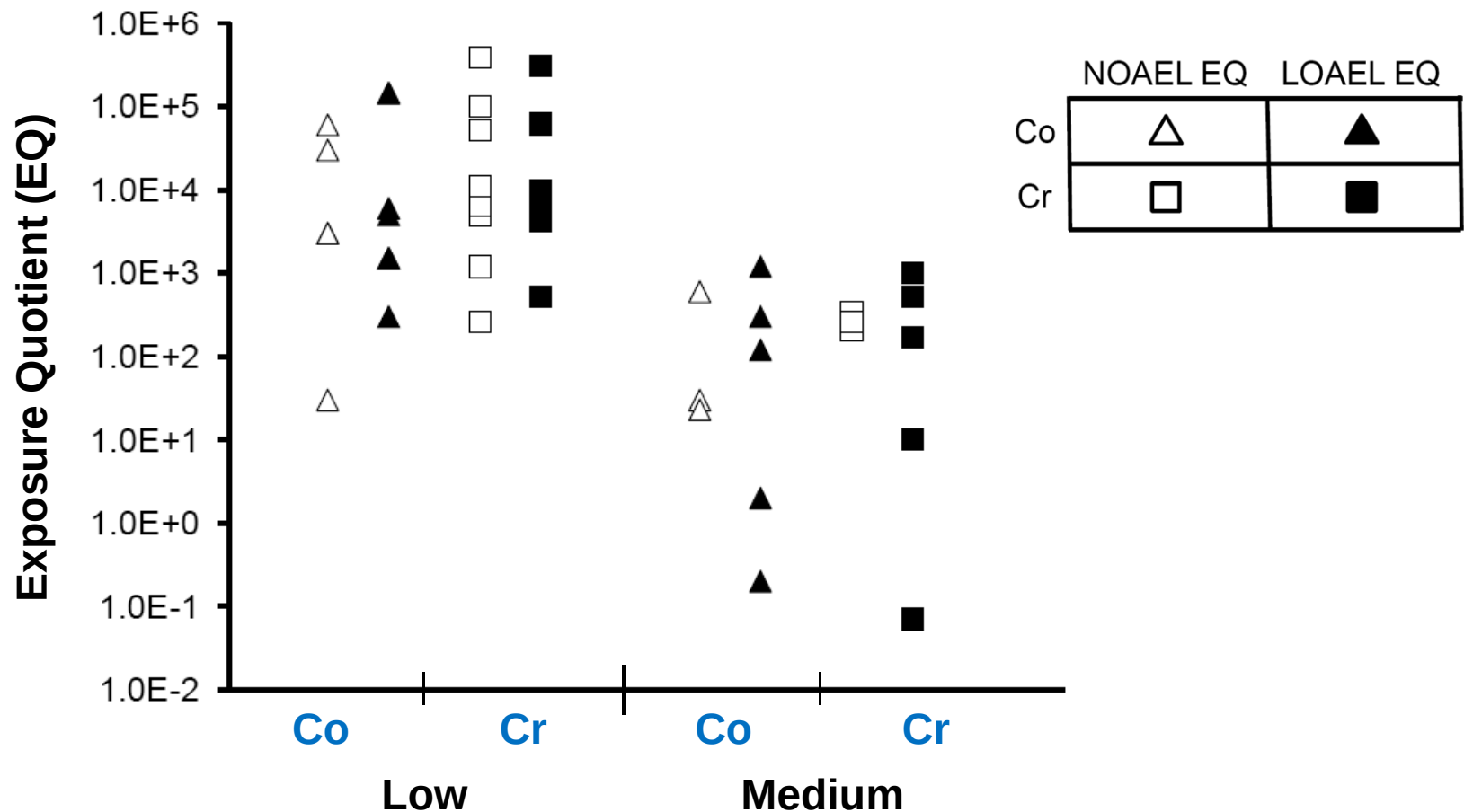
- ***The greater the EQ value, the lower the likelihood of genotoxicity or carcinogenicity occurring as a result of exposure to wear debris***



Exposure quotients from *in vitro* assays with Co/Cr soluble ions

Risk characterization

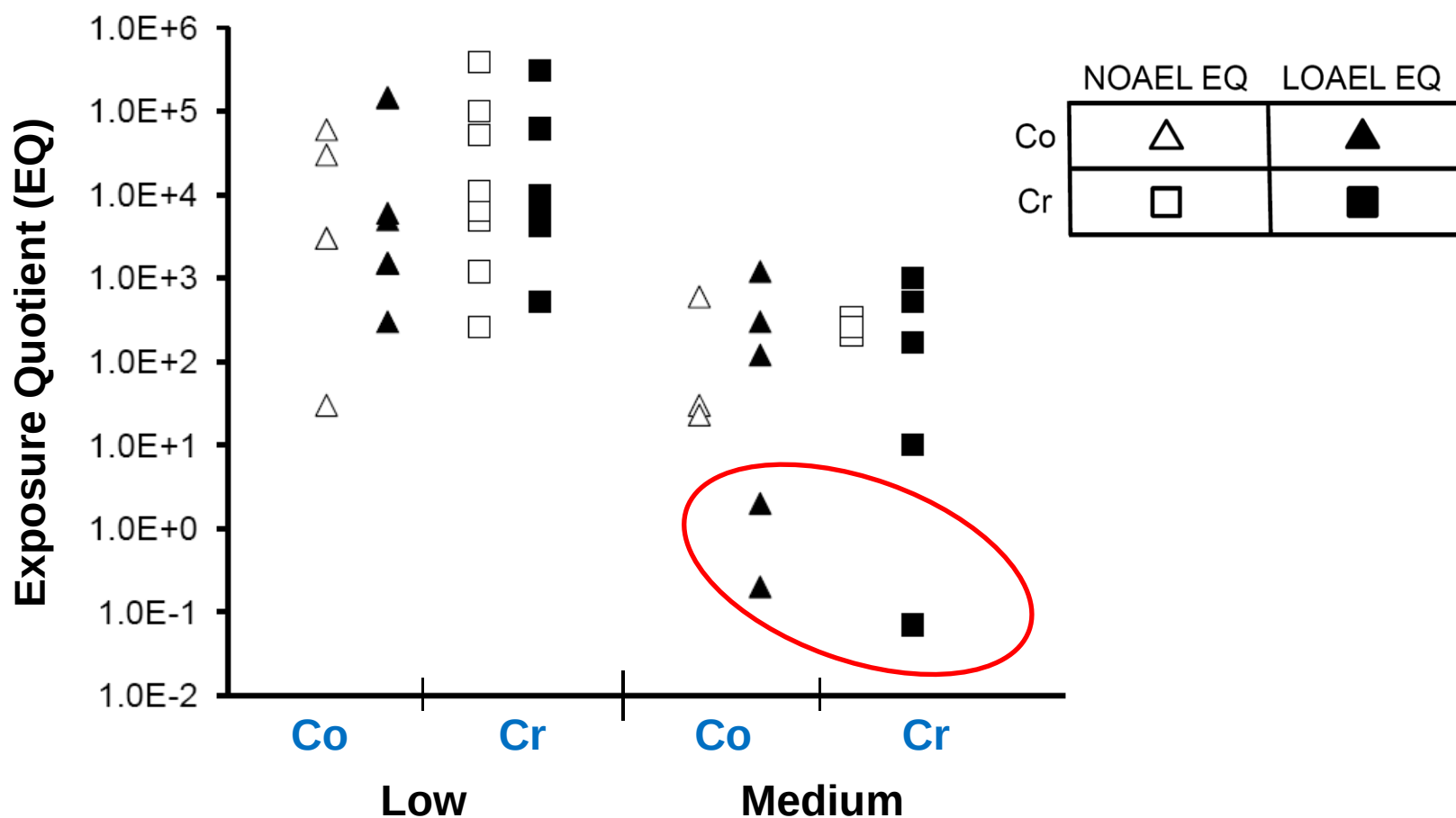
➤ Category 1 – *in vitro* assays with Co/Cr soluble ions



Exposure quotients from *in vitro* assays with Co/Cr soluble ions

Risk characterization

➤ Category 1 – *in vitro* assays with Co/Cr soluble ions



Outliers from *in vitro* assays with Co/Cr soluble ions

Risk characterization

➤ Category 1 – *in vitro* assays with Co/Cr soluble ions

➤ *Figgitt et al., 2010*

➤ Chromosomal aberrations in fibroblasts

➤ Co 0.3 µg/L

➤ Cr(III) 0.36 µg/L

➤ Below 7 µg/L MHRA guideline

➤ Dietary/background blood levels pose a significant risk of DNA damage

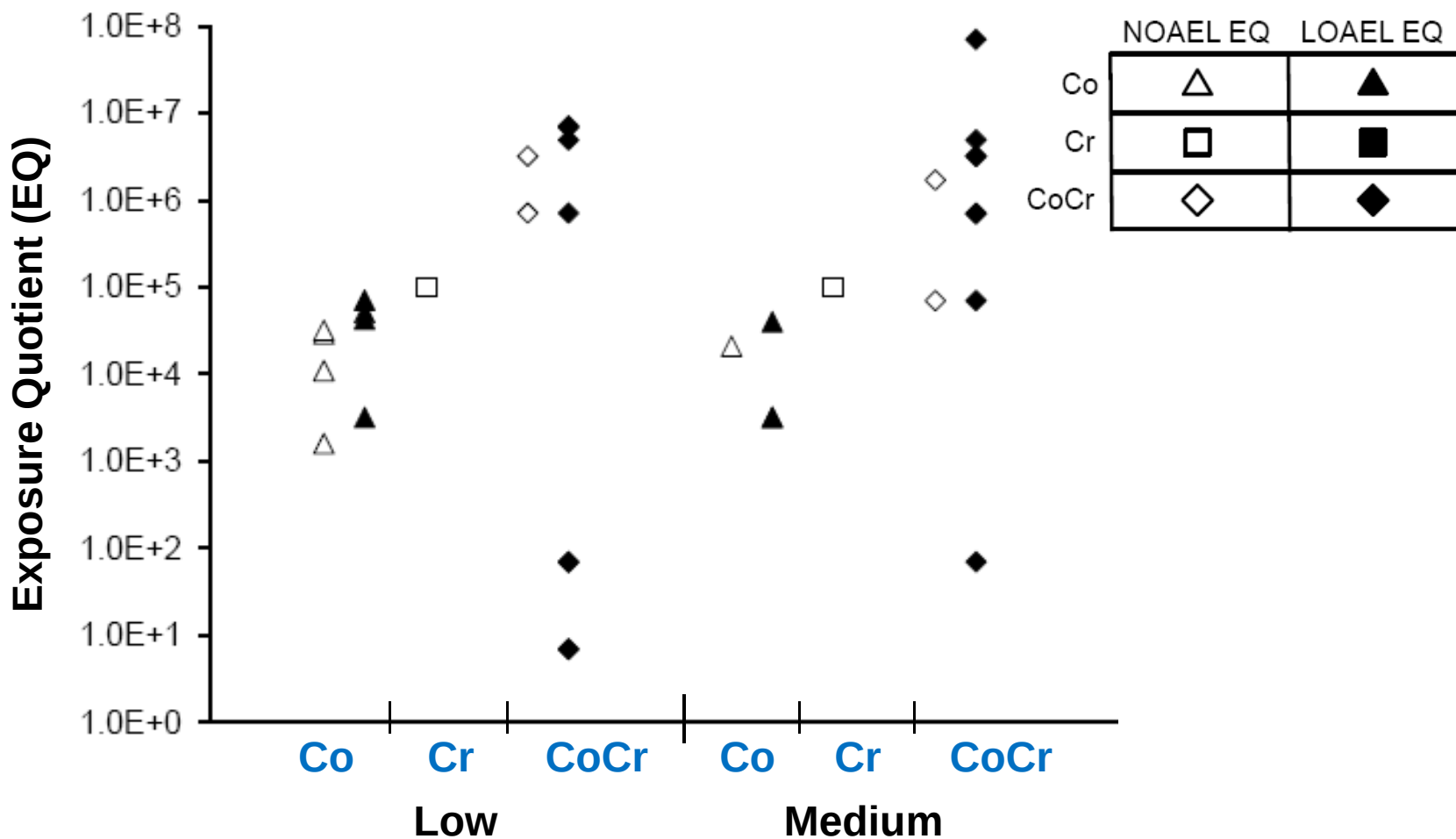
➤ BJ fibroblasts

➤ Cell-type specific response

Exposure quotients from *in vitro* assays with Co/Cr particulates

Risk characterization

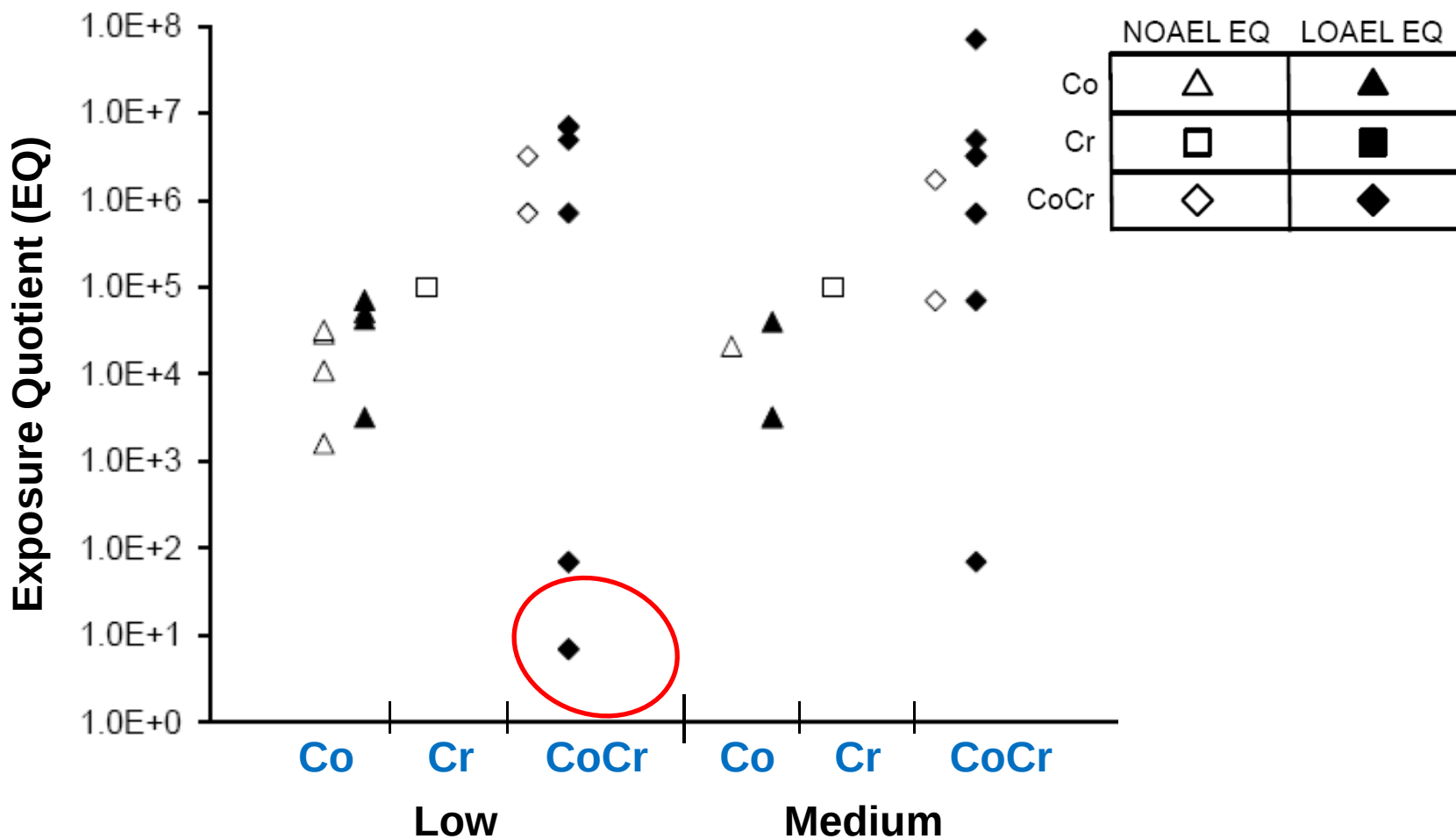
➤ Category 2 – *in vitro* assays with Co/Cr particulates



Exposure quotients from *in vitro* assays with Co/Cr particulates

Risk characterization

➤ Category 2 – *in vitro* assays with Co/Cr particulates



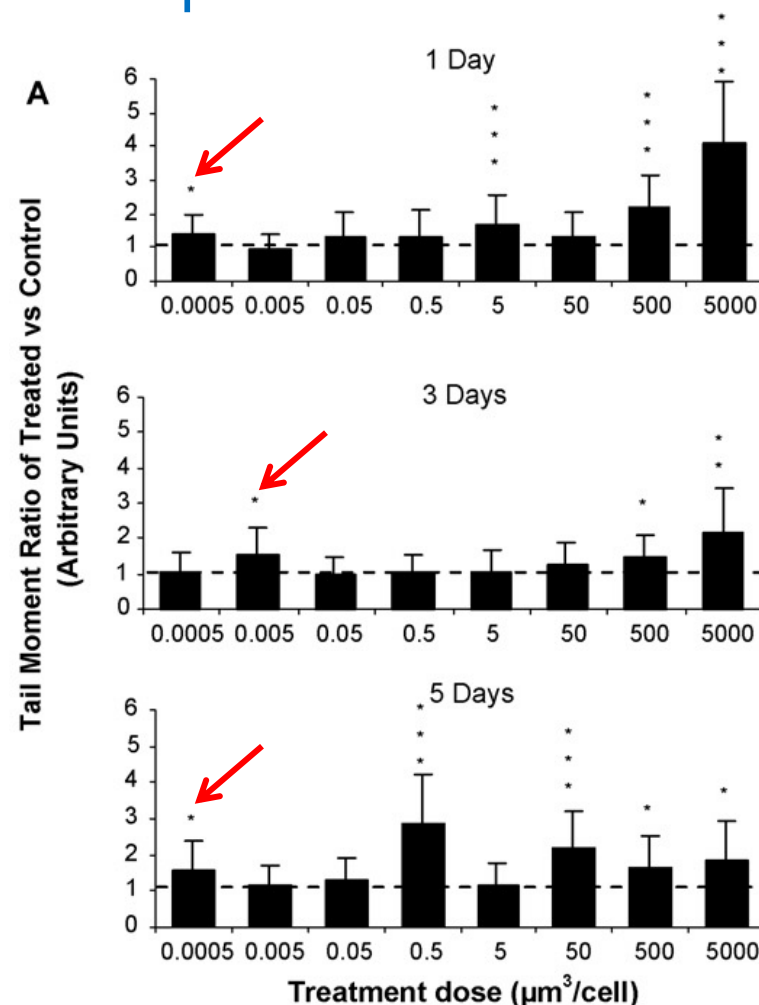
Outliers from *in vitro* assays with Co/Cr particulates

Risk characterization

➤ Category 2 – *in vitro* assays with Co/Cr particulates

➤ Papageorgiou et al., 2007

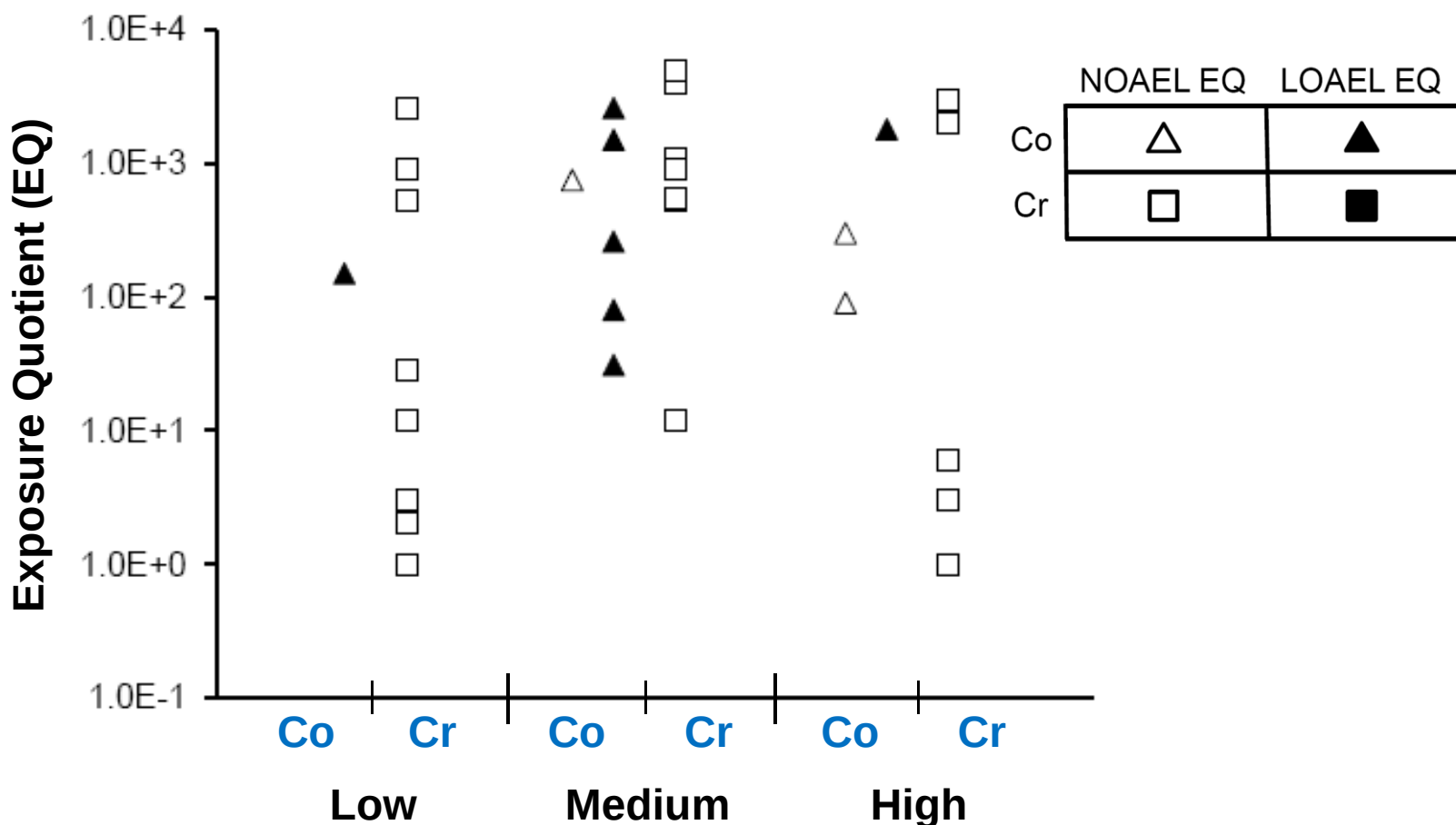
- Anomalous LOAELs
- Wrong statistical methodology
 - Quantal vs. continuous data
 - ANOVA required



Exposure quotients from *in vivo* assays with Co/Cr soluble ions

Risk characterization

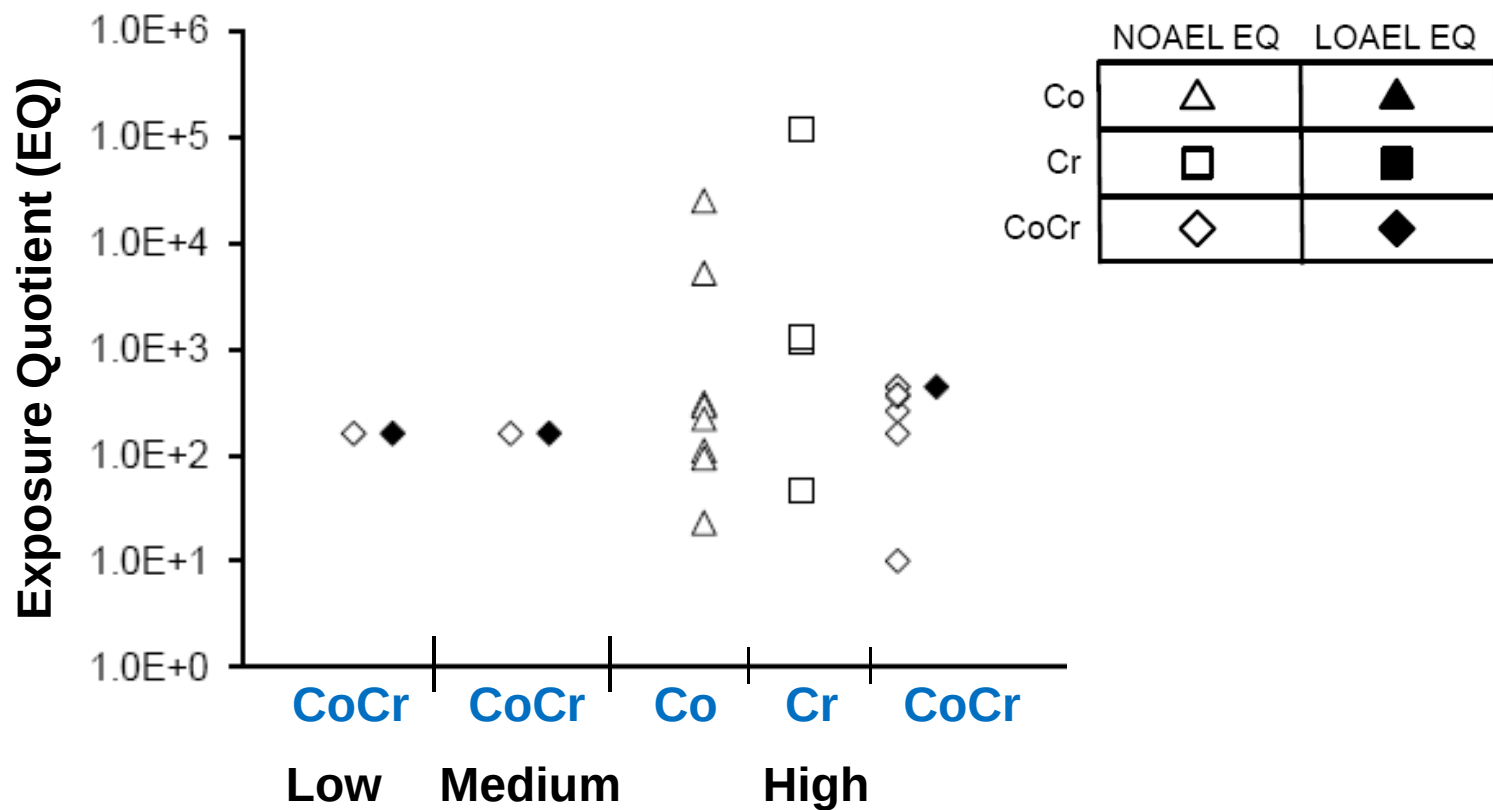
➤ Category 3 – *in vivo* assays with Co/Cr soluble ions



Exposure quotients from *in vivo* assays with Co/Cr particulates

Risk characterization

➤ Category 4 – *in vivo* assays with Co/Cr particulates



Solid state carcinogenesis was found to be largely negative

Risk characterization

- Foreign-body carcinogenesis or the “Oppenheimer effect”
 - Fairly common regardless of the implanted material
 - Unique to rodents, not predictive of cancer risk in humans
 - TBCC Table 7:

“No significant increase in implantation site or systemic tumors above controls”

- Only ~21 local malignancies ever reported in patients with CoCr-containing hip implants



Conclusions

Risk characterization

- The WOE suggests that the concentration of wear debris in MoM patients is too low to increase systemic cancer risks
 - “Worst case” systemic tissue levels of Co/Cr particles are typically **thousands of times lower** than the levels required to cause DNA effects *in vitro* and *in vivo*
 - Experimental doses are not physiologically relevant
- To date, our findings agree with epidemiology studies assessing systemic cancers in MoM hip implant patients
 - Incidence in 1st generation and contemporary MoM devices

Uncertainties and limitations of our analysis

Risk characterization

- Estimation of tissue particle doses and concentrations
 - Conservatively over-estimated
 - Dissolution of ions
 - Particle excretion does occur
- Estimation of LADDs for single injection studies
 - Over-estimated
 - Very slow rate of particulate elimination
 - Some particulate remained at injection sites in animals
 - Tumor EQ values biased high
- False negatives and positives
 - Surely occurred, but difficult to account for

Closing comments

- We are currently involved in an epidemiology study
 - Expect that future epidemiology studies and respective product-specific safety databases to reach conclusions consistent with ours
- Could this type of study help with ISO 10993-3 testing requirements?

“Scientifically sound alternatives to the proposed testing may be acceptable insofar as they address relevant matters of safety assessment” (p. vi)

“Carcinogenicity testing shall not be performed when risks can be adequately assessed or managed without generating new carcinogenicity test data” (p. 5)

Acknowledgements

- Society of Toxicology Medical Device and Combination Product Specialty Section
 - Kelly Coleman, PhD, DABT, RAC
- Cardno ChemRisk
 - Jackson Hole – Dennis Paustenbach, PhD, CIH, DABT
 - NYC – Brent Finley, PhD, DABT
 - Boulder – Lindsay Oliver, MPH & Brooke Tvermoes, PhD
 - San Francisco – Andy Monnot, PhD
 - Pittsburgh – Julie Panko, CIH & Marisa Kreider, PhD, DABT

Questions

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