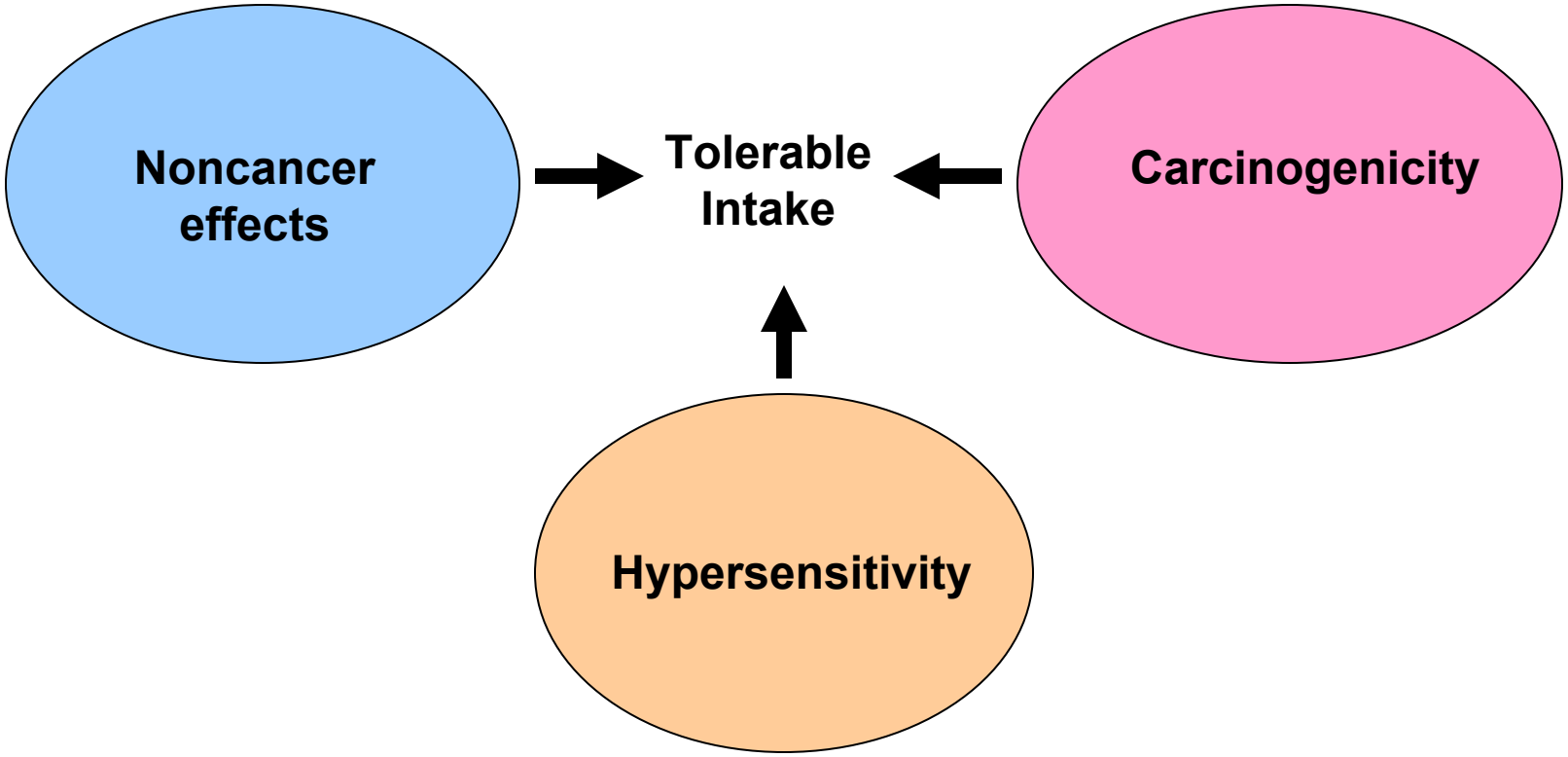
Scientific approach to development of TI levels for nickel released from nickel-containing cardiovascular devices

Ron Brown
Rosalie Elespuru
Jennifer Goode
Nicole Ibrahim

March 9, 2012

Are sufficient data available to establish Tolerable Intake values for nickel by parenteral routes of exposure?



What is a Tolerable Intake (TI) value?

- Tolerable Intake = Dose (mg/kg/day) below which adverse systemic effects are not likely to occur in exposed patients:
  - Equivalent to other types of Health-Based Exposure Limits (e.g., ADI, TDI, RfD, etc.).
  - Can be based on noncancer and carcinogenic effects.
  - Not intended to be protective for all adverse effects (e.g., hypersensitivity, local effects at the site of an implant).
  - Derived using approach outlined in the ISO 10993-17 standard.

Why do we need a TI value for parenteral nickel?

- Part of the process to evaluate the safety of nickel-containing devices.
- Determine the need for improvements in device design/engineering.
- Provide scientific support for risk management decisions (e.g., help to determine need for labeling).

Discussion questions

Noncancer effects

- What toxicity data should serve as the basis for the TI?

Hypersensitivity

- Is it appropriate to set a TI for nickel based on hypersensitivity?
- What are the potential merits and difficulties with screening patients pre-operatively for nickel allergy?

Carcinogenicity

- Can we establish a cancer-based TI for soluble nickel based on available data?

Noncancer effects of nickel

- Exposure of experimental animals to soluble nickel salts or metal ions has resulted in a wide range of adverse effects:
  - Nephrotoxicity/hepatotoxicity
  - Cardiovascular effects
  - Metabolic effects

- The results of studies in experimental animals (and exposed humans) form the basis for acceptable levels of exposure to chemical compounds.

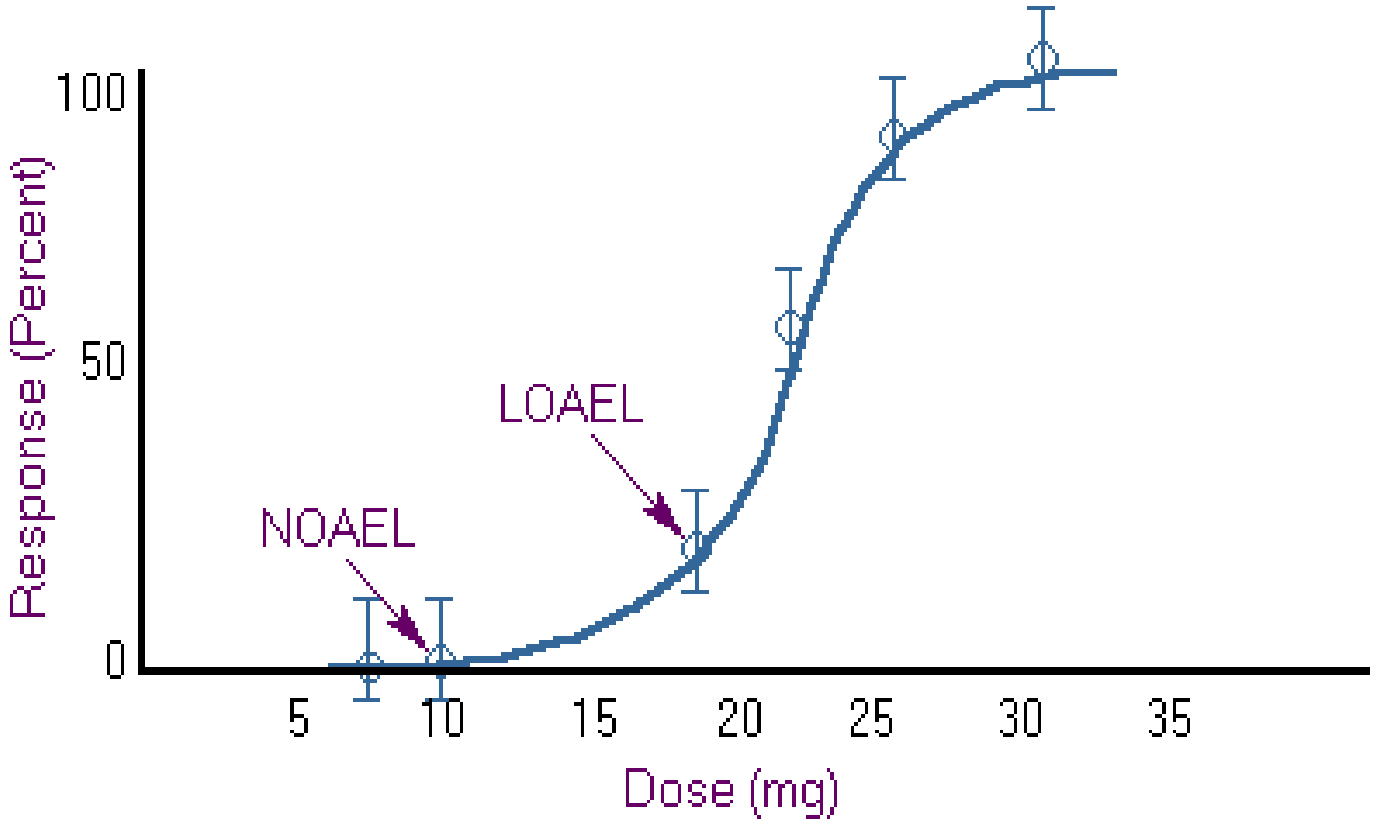
How do we derive TI values?

- General approach in ISO 10993-17 standard is consistent with that used by regulatory agencies and advisory groups (e.g., WHO, US EPA, ICH) to set exposure limits for environmental pollutants, food additive, impurities in pharmaceutical products.
  - While Part 17 is not currently recognized by FDA, this approach has been used on a case-by-case basis for device risk assessment

- Steps to derive a noncancer TI:
  1. Identify the toxicity study reporting adverse effects occurring at the lowest doses (find most sensitive endpoint).
  2. Apply uncertainty factors to account for differences in potency between animals and humans and for variability in the human population.

NOAEL and LOAEL

NOAEL = No Observed Adverse Effects Level
LOAEL = Low Observed Adverse Effects Level



Generic example (not specific to nickel)

Available dose-response data for nickel

- FDA searched the literature to identify all relevant toxicity studies for nickel.
- Focused on studies by parenteral routes of exposure.
- For oral exposure studies, conducted route-to-route extrapolation of dose to estimate absorbed dose.
- Considered both single- and repeat-dose studies.
- Identified key studies based on the quality of the study and the dose that produced the effects.

Single-dose parenteral toxicity studies of soluble nickel

IV = intravenous

SC = subcutaneous

IP = intraperitoneal

Study	Nickel compound	Route	Species	NOAEL (mg/kg)	LOAEL (mg/kg)	Effect
Rubanyi et al (1984)	$NiCl_2$	IV	Dog	None	0.02	Increased coronary artery resistance
Ligeti et al. (1980)	Ni Ion	IV	Dog	None	0.02	Reduction of coronary blood flow and cardiac contractility
Horak and Sunderman (1975)	$NiCl_2$	IP	Rat	0.5	0.7	Hyperglycemia
Harkin et al. (2003)	$NiCl_2$	IP	Rats	None	1	Reduced weight gain, altered thermoregulation
Foulkes and Blanck (1984)	$NiCl_2$	?	Rabbits	None	1.18	Reduced absorption of aspartate in kidney
Gupta et al. (2000)	$NiCl_2$	IP	Rats	None	1.5	Hyperglycemia
Mas et al. (1985)	$NiCl_2$	IP	Rats	1	2	Reduced fetal weight
Gitlitz et al. (1975)	$NiCl_2$	IP	Rat	None	2	Nephrotoxicity, proteinuria
Horak et al. (1976)	$NiCl_2$	IP	Rat	None	2.7	Dose lethal to 5% of animals (LD5)
Gordon (1989)	$NiCl_2$	IP	Rat	1.5	3	Altered thermoregulation
Xie et al. (1995)	$NiCl_2$	IP	Mice	1	5	Decreased fertility rate, increased testicular lipid peroxidation
Xie et al. (1996)	$NiCl_2$	IP	Mice	1	5	Pulmonary toxicity

Derivation of a short-term parenteral TI value for nickel

- NOAEL values: 0.5 – 1 mg/kg/day
- LOAEL values: 1 – 3 mg/kg/day
- Weight of evidence suggests the use of a NOAEL value on the order of 1 mg/kg/day
  - Multiple studies, robust endpoints

Provisional short-term parenteral TI

For a TI of 1000 µg/kg/day ÷ 100 (MF) = 10 µg/kg/day

MF = Modifying Factor = product of uncertainty factors

TI = Tolerable Intake

Repeat-dose parenteral studies

Study	Compound	Route	Species	Dosing regimen	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect
Wang (2002)	NiCl2	IP	Rats	1/day x 7 days	0.045	0.45	↑ BP
Pereira (1998)	Aqueous solution of metallic nickel	SC	Mice	1/day on days 0, 7, 14 and 21	None	0.3	Kidney Liver

Provisional long-term TI values based on repeat-dose parenteral studies

Study	Compound	Route	Species	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	MF	TI* (μg/kg/day)
Wang 2002	NiCl2	IP	Rats	0.045	0.45	↑ BP	100	0.5
Pereira 1998	Aqueous solution of metallic nickel	SC	Mice	None	0.3	Kidney Liver	300	1

*Provisional TI

Health Based Exposure Limits (HBELs) values based on data from repeat-dose oral studies

Study	NOAEL	LOAEL	Endpoint	MF	Oral exposure value (μg/kg/day)	Agency/group using study as basis for exposure level
Ambrose et al. (1976)	5	50	Decreased body weight and organ-to-body weight ratios	300	20	US EPA
Vyskocil et al. (1994)	None	7.6	Increased urinary albumin	1000	8	TERA
Heim et al. (2007)	2.2	6.6	Decreased body weight gain, hematology changes	100	22	
NiPERA (2000)	1.12	2.23	Increased pup death	100	11.2	OEHHA
Smith et al. (1993)	None	1.3	Increased pup death	1000	1.3	Health Canada

Parenteral TI values for nickel based on oral HBELs derived by other regulatory agencies

Regulatory agency/advisory group	Oral exposure level (μg/kg/day)	Route	Oral-parenteral conversion factor[1]	Provisional parenteral TI (μg/kg/day)
Health Canada	1.3	Drinking water	0.25	0.4
US EPA	20	Feed	0.03	0.6
TERA	8	Drinking water	0.25	2
OEHHA	11.2	Gavage	0.25	2.8

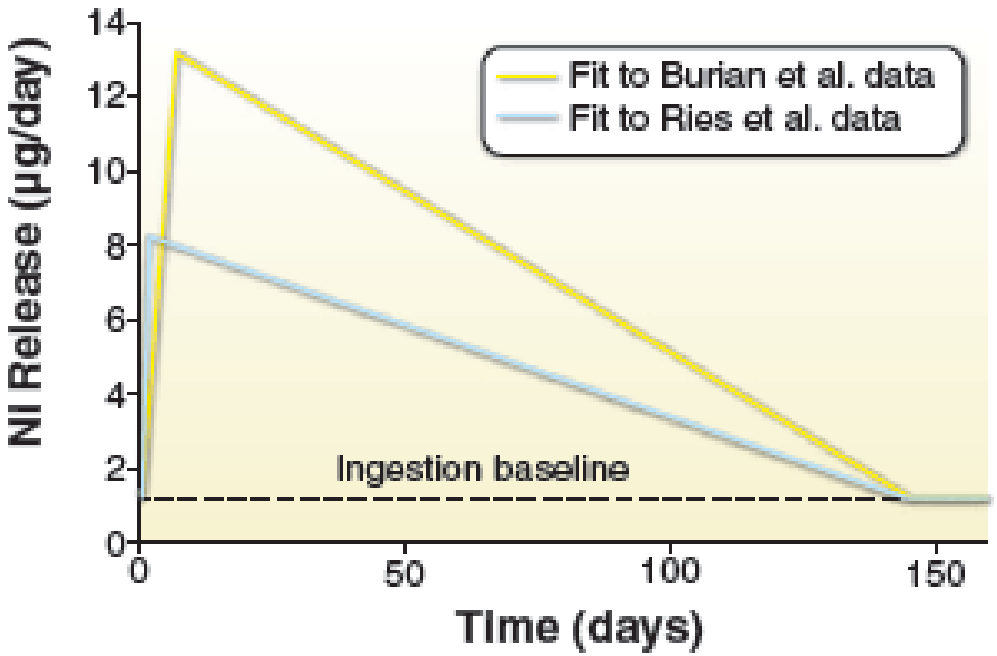
[1]Assumed 3% oral absorption from feed and 25% absorption from drinking water and gavage (ATSDR, 2005)

Comparison of HBELs for nickel derived by regulatory agencies and standards groups

Regulatory Agency/Advisory Body	Type of exposure limit	Exposure limit value (μg/kg/day)
FDA/CDRH	Short- and long-term TI for parenteral exposure to soluble nickel released from medical devices	Under review
US Pharmacopeia (USP)	The Permissible Daily Exposure (PDE) for nickel as a metallic impurity in drug products	0.5
Sunderman (1983)	Dose corresponding to recommended level for nickel in intravenous solutions	0.5
US EPA	Estimated parenteral dose equivalent to the Reference Dose (RfD) for soluble nickel	0.6
FDA/CFSAN	Parenteral dose received following consumption of bottled water containing nickel at the maximum allowable limit	0.7

Risk characterization: Compare Noncancer TI and dose

For a TI of 0.5 µg/kg/day x 70 kg (adult) = 35 µg/day



Tsuji et al. (2011) presented at the Society of Toxicology meeting

Figure 3.

Modeled Ni release rates predicted by serum levels of patients after implantation of cardiac occlusion devices. Triangular Ni release rate functions result in the biokinetic model fits to serum Ni concentrations in Figure 2, based on data from Ries et al. (2003) and Burian et al. (2006). Dashed line denotes Ni release to serum from background ingestion.

HW: How much nickel do you typically see being released from your device(s) in vitro?

For a TI of 0.5 µg/kg/day x 70 kg (adult) = 35 µg/day

For nitinol devices:

Device Surface Area (min max, median)	0.9, 50.13, 5.3 cm^2	n=8
Minimum peak release rate (range)	0.19-2.89 µg/day	n=5
Maximum Peak release rate (range)	0.42-8.40 µg/day	n=5
Average peak release rate (range)	0.043-4.8 µg/day	n=7
Time to Peak release (min, max, median)	<1, 30, 3.5 days	n=12
Peak release acceptance criteria (range)	35-670 µg/day	n=6
Minimum chronic release rate (range)	<0.015-0.63 µg/day	n=7
Maximum chronic release rate (range)	<0.015-1.72 µg/day	n=7
Average chronic release rate (range)	<0.015-1.31 µg/day	n=7
Minimum Total Release (range)	2.0-80 µg	n=6
Maximum Total Release (range)	5.13-140 µg	n=6
Average Total Release (range)	0.11-110 µg	n=9

Summary

Available data suggest for noncancer effects:

- Short-term (<24hrs) parenteral TI: ~ 10 µg/kg/day
  - Weight of evidence approach

- Long-term (>24hrs) parenteral TI: ~ 0.5 µg/kg/day
  - From repeat-dose parenteral studies
  - From HBELs derived by other regulatory agencies

Adult TI ~ 0.5 µg/kg/day x 70 kg ~ 35 µg/day

Pediatric TI ~ ?

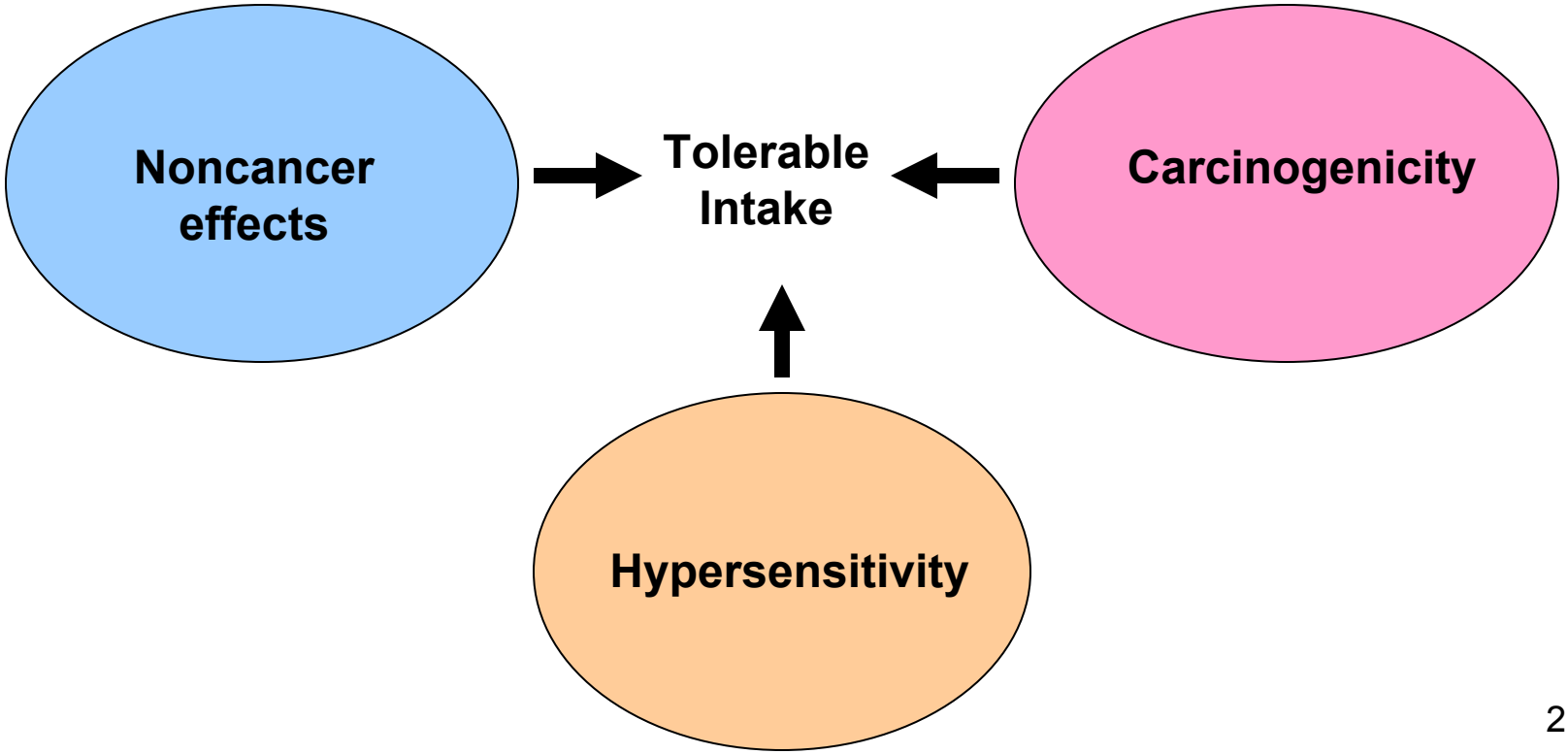
Discussion questions (10 min)

Noncancer effects

- Are the data in the literature sufficient/ appropriate for the derivation of a noncancer TI (with the exception of data on hypersensitivity)?

- Is the approach used to derive a provisional noncancer TI for nickel appropriate?

Are sufficient data available to establish Tolerable Intake values for nickel by parenteral routes of exposure?



Hypersensitivity

- Up to 17% of women and 3% of men are sensitized to nickel

  Thyssen JP et al, Contact Dermatitis 2007;57:287–99

- Questions have been raised about whether patients with nickel allergy are at increased risk for developing complications after implantation of nickel-containing devices

Discussion questions (5 min)

Hypersensitivity

- Should hypersensitivity serve as an endpoint for derivation of a TI value?

  NOTE: Hypersensitivity is not typically used as the basis for setting exposure limits, since some patients may be particularly sensitive to the allergic effects of chemical compounds and the TI would not necessarily be protective for these effects.

Discussion questions (15 min)

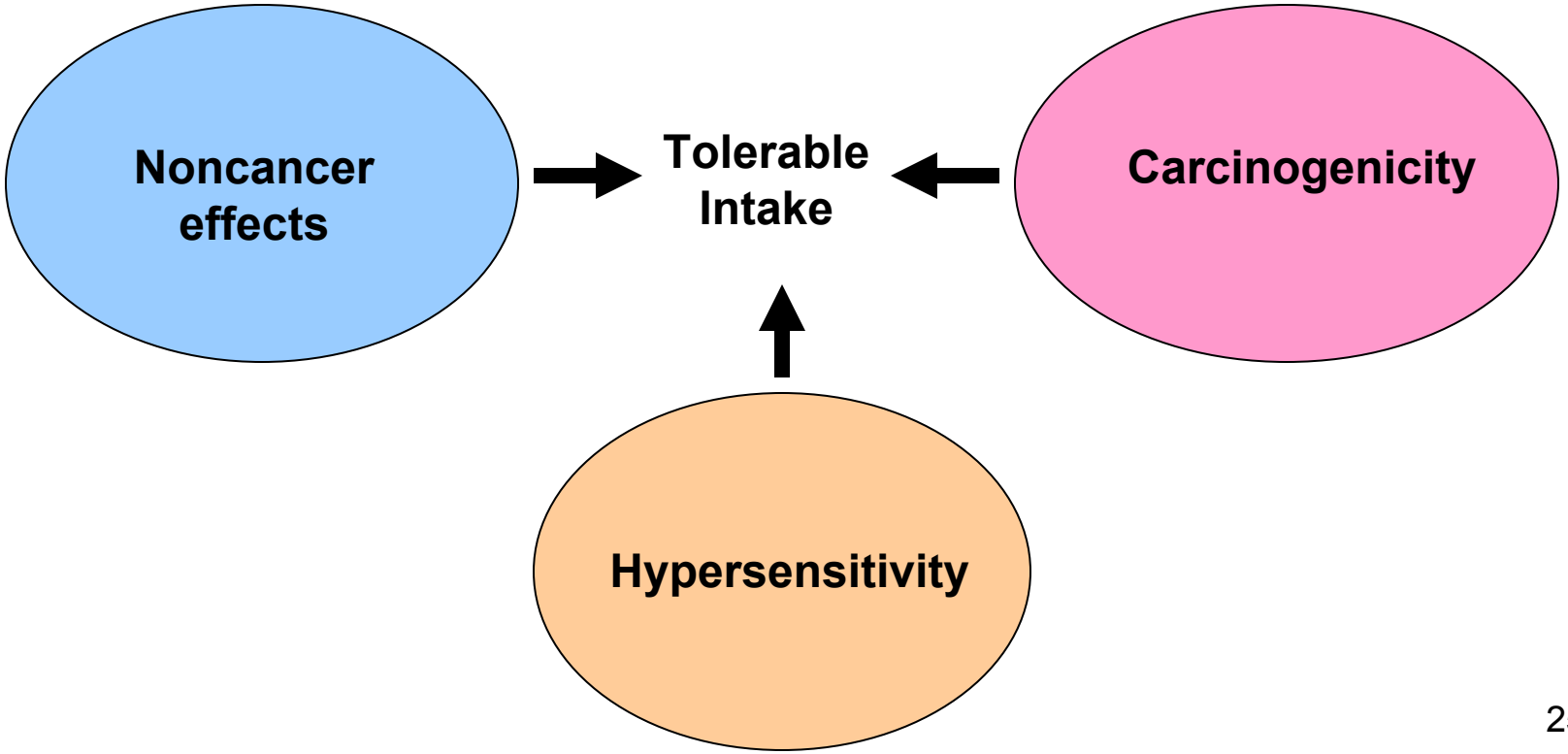
Pre-operative screening for hypersensitivity

- Patients are not routinely screened for metal allergy before receiving nickel-containing cardiovascular implants. Discuss the potential merits and drawbacks of:
  - Routine screening for metal allergy in all patients.
  - Screening for metal allergy in patients with suspected nickel allergy/hx of dermatitis.

- For some orthopedic devices, screening for metal allergy is conducted. Are screening considerations different for patients with nickel-containing intravascular devices vs. orthopedic devices?

- If metal allergy screening is performed, what are commonly used screening methods, and the potential merits and drawbacks of these screening methods?

Are sufficient data available to establish Tolerable Intake values for nickel by parenteral routes of exposure?



Cancer-based TI for nickel

<u>Insoluble nickel</u>

- Widely considered to be carcinogenic by inhalation, oral routes.

<u>Soluble nickel</u>

- Not carcinogenic by oral exposure, but has been shown to be a complete carcinogen after IP injection in animal studies.

Proposed mechanism for the carcinogenicity of nickel based on bioavailability to the nucleus

Goodman et al. (2011)

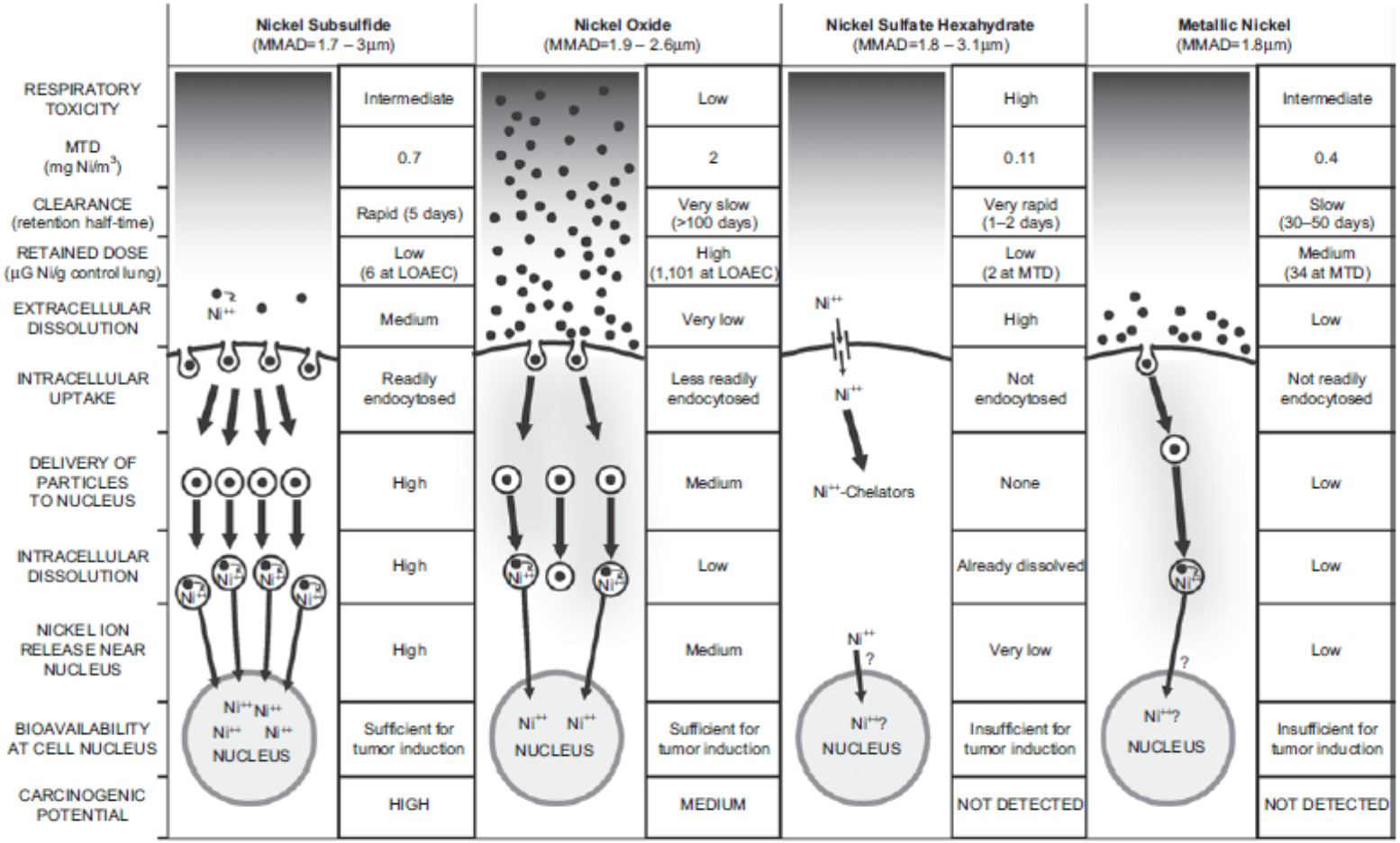


Figure 1. The nickel ion bioavailability model takes into account the various factors that determine the bioavailability of the nickel ion at the nucleus of target cells *in vivo*. The examples in this figure are based on the results of *in vitro* and *in vivo* mechanistic studies as well as the rat inhalation bioassays with nickel-containing substances.

Available studies on the carcinogenicity of soluble nickel by parenteral routes

Studies	Route	Limitations
Kasparak et al., (1990); Poirier et al., (1984); Stoner et al., (1976)	IP	Used Stain A mouse. Useful for hazard identification, but results from this very sensitive animal model are not typically used for setting TI values.
Diwan et al (1992)	IP	Only single dose used, relatively small sample size used for a carcinogenicity study (n=30 instead of 50 typically used in NTP studies), thorough histopathological examination not performed.
Pott et al. (1992)	IP	Not published in a peer-reviewed journal, only local tumors were assessed, relatively small sample size (n ≈ 30).

IP = Intraperitoneal

Discussion questions (10 min)

Cancer-based TI

- Can we establish a cancer-based TI for soluble nickel based on available data? If so, are there data in the literature that are appropriate for the derivation of a cancer-based TI that have not been considered?

- Is the inhalation nickel-ion bioavailability model of Goodman et al. (2011) useful for determining the carcinogenic potential of nickel released from nickel-containing alloys used for medical devices?