The 52nd William Blum Lecture
Presented at NASF SUR/FIN 2015
in Rosemont, Illinois
June 8, 2015

Nickel: Science, Health and the Future

by
Dr. Hudson Bates
Recipient of the 2014 William Blum
NASF Scientific Achievement Award

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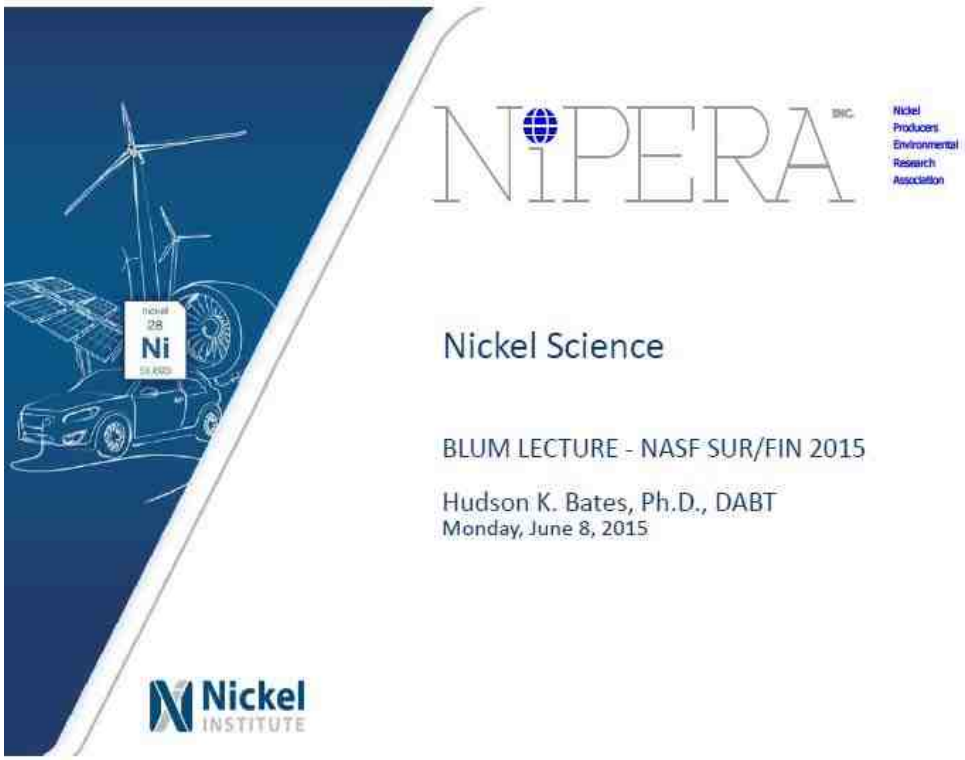
Editor's Note: The following is the Powerpoint presentation by Dr. Bates in delivering his William Blum Memorial Lecture at SUR/FIN 2015, in Rosemont, Illinois on June 8, 2015.



What is the Nickel Institute?

NiPERA

Ambatovy
ANGLO AMERICAN
ANGLO PLATINUM
Aurubis
Bochemie
bhpbilliton
ERAMET
GlencoreXstrata
lundin mining
NORILSK NICKEL
PACIFIC METALS CO., LTD.
sherritt
SINOSTEEL
SUMITOMO METAL MINING CO., LTD.
TALVIVAARA
umicore
VALE
Vale Canada Limited
PT Vale Indonesia
Tbk
Vale Japan Limited
WESTERN AREAS NL

Approximately 85% of worldwide nickel production outside China

What is NiPERA?

NiPERA

- Science branch of the Nickel Institute
- Offices in Durham, North Carolina, USA
- Human health toxicologists (4) and ecotoxicologists (2)
- Manage research on health and environmental effects of nickel and nickel substances
- Perform risk assessments to support global regulatory obligations
- Communicate knowledge on fate and effects of nickel to global regulatory community

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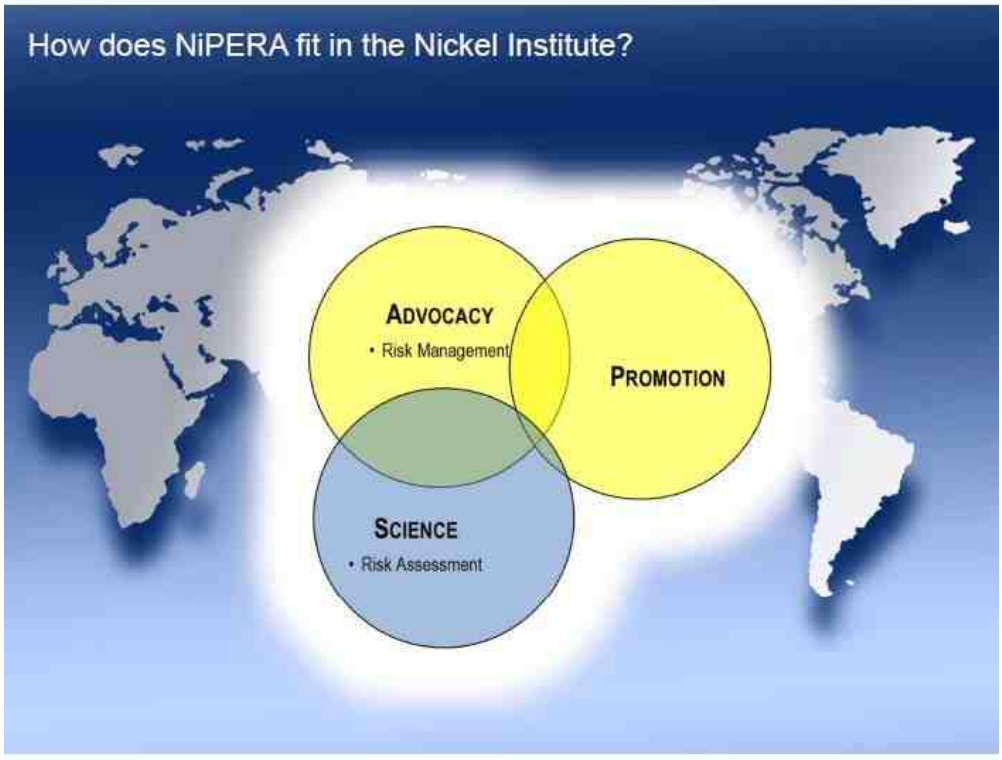
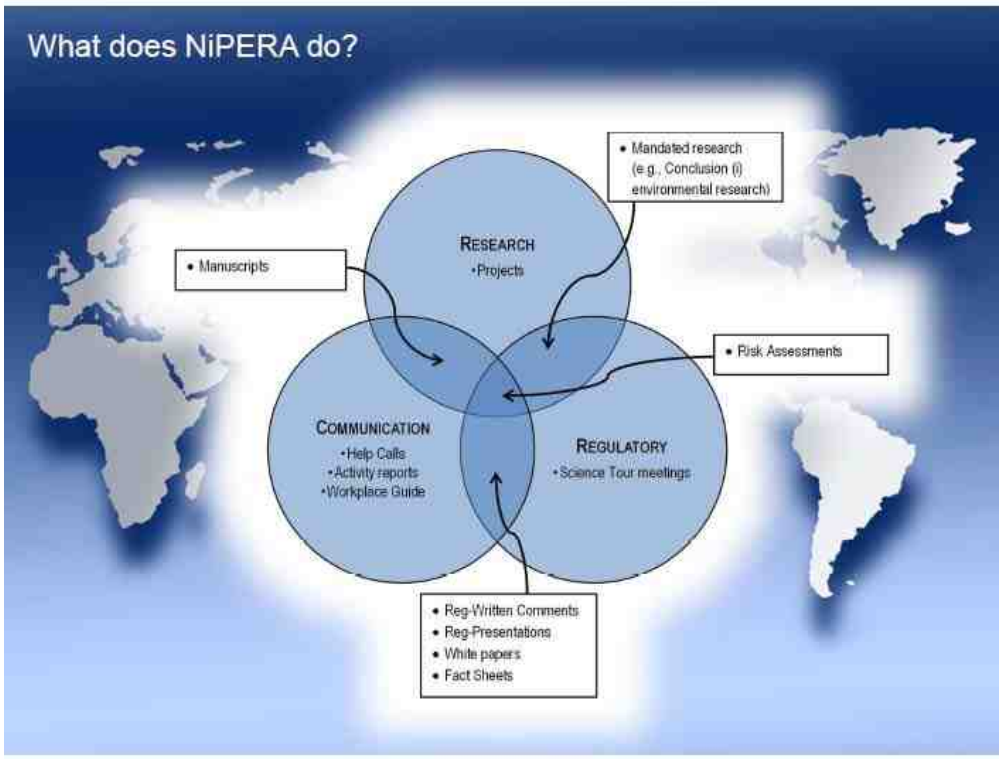
Who is NiPERA?


How does NiPERA fit in the Nickel Institute?
ADVOCACY
• Risk Management
PROMOTION
SCIENCE
• Risk Assessment


What does NiPERA do?
• Mandated research (e.g., Conclusion (i) environmental research)
• Manuscripts
RESEARCH
•Projects
• Risk Assessments
COMMUNICATION
•Help Calls
•Activity reports
•Workplace Guide
REGULATORY
•Science Tour meetings
• Reg-Written Comments
• Reg-Presentations
• White papers
• Fact Sheets


What we do – HEALTH & ENVIRONMENTAL RESEARCH!
• 2015 - 124 Funded Research Projects


What we do – REGULATORY!
• Over 200 regulatory comments in the past decade!


What we do – COMMUNICATION!
• 52 Manuscripts & 3 Book Chapters in recent years
Safe Use of Nickel in the Workplace
HEALTH GUIDE
1
Fact Sheet
European Union Environmental Risk Assessment of Nickel
Data Compilation, Selection, and Derivation of PNEC Values for the Freshwater Compartment
2
Fact Sheet
European Union Environmental Risk Assessment of Nickel
Data Compilation, Selection, and Derivation of PNEC Values for the Soil Compartment
3
Fact Sheet
European Union Environmental Risk Assessment of Nickel
Data Compilation, Selection, and Derivation of PNEC Values for the Marine Aquatic Compartment
4
Fact Sheet
European Union Environmental Risk Assessment of Nickel
Incorporation of Bioavailability in the Aquatic Compartment
5
Fact Sheet
European Union Environmental Risk Assessment of Nickel
Incorporation of Bioavailability in the Terrestrial Compartment
6
Fact Sheet
European Union Environmental Risk Assessment of Nickel
SECONDARY POISONING RISK ASSESSMENT OF BIRDS

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Nickel Toxicity

Short History of Nickel Toxicology

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- 1889-1930: The first modern association of nickel exposure with adverse health effects in workers occurred in the anecdotal observation of nickel dermatitis in workers in the nickel plating industry
- 1902: Start of the Mond refining process at the Clydach refinery in Wales. The process used nickel carbonyl and poisoning effects associated with accidental exposure had to be dealt with
- 1930s: First appearance of nickel dermatitis in consumers
- 1920s & 30s: Sino-nasal and lung cancers in some nickel refinery workers at the refinery in Clydach, Wales altered physicians to the possibility of respiratory cancer resulting from long-term exposure to nickel compounds.
- 1950s: Medical Research confirmed cancer findings and the observation of additional groups of workers involved in roasting, sintering, and calcining operations at refineries in Kristiansand Norway, and Ontario Canada.
- 1960s & 70s: The first reports of a possible developmental toxicity effect of nickel in animal studies were published.

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Nickel Toxicity – Main Effects

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- Main Health Effects Associated With Nickel Exposures

Health Effect	Route of Exposure	Nickel Species
Respiratory Effects (*e.g.*, fibrosis, chronic bronchitis, asthma)	Inhalation	Soluble, Sulphidic (Metal, Oxidic)
Respiratory Cancer (nasal and lung)	Inhalation	Sulphidic, Oxidic, Soluble (during refining of sulphidic ores)
Reproductive Effects*	All routes	Soluble
Dermatitis	Dermal	Soluble, Metal

* From animal data

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Nickel Toxicity – Carcinogenesis

Research Area: Determine Appropriate Nickel Compound Carcinogen Classifications

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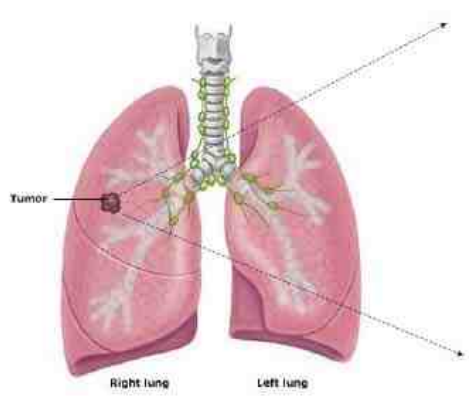

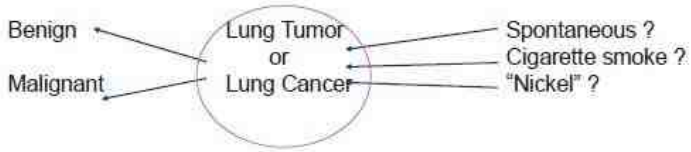

Appropriate Nickel Compound Carcinogen Classifications: Why is it important to get it right?

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- To protect the workforce and public from risks associated with exposure to nickel compounds
- Carcinogen Classifications
  - Affect workplace regulations and workers' protection
  - Affect ability to market and use products
- Exposure Levels Associated with Carcinogenicity
  - Affect workplace regulations and workers' protection
  - Affect allowable air levels for general population

Nickel Toxicity – Human Carcinogenesis

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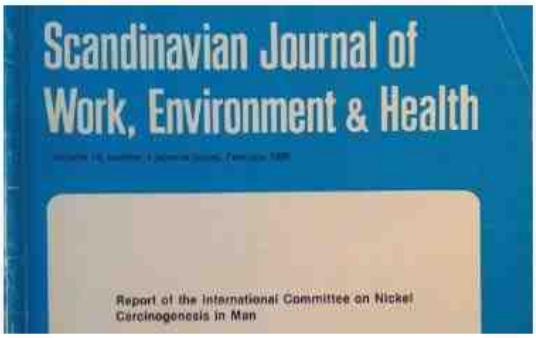
- Respiratory Cancer
  - Studies of workers involved in the refining of lateritic ores have not shown an association between excess respiratory cancer and nickel exposures (mainly nickel silicate oxides, complex Ni oxides).

  - **No other site except respiratory tract**
  - **No other route of exposure except inhalation**



Nickel Toxicity – Animal Carcinogenesis

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- Respiratory and Systemic Cancer

  - An animal study with nickel metal powder was finished in 2008. It shows no respiratory cancer after lifetime (24-months) exposure to 1.6 MMAD nickel particles.
    - Animal = Human

  - An oral carcinogenicity study with nickel sulfate hexahydrate (2005) did not show any systemic carcinogenicity
    - Animal = Human

Nickel Toxicity – Human Carcinogenesis

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- Respiratory Cancer
  - Animal studies confirm human observations for **Nickel Compounds** as carcinogens (except sulfate)
  - Animal studies confirm the **lack** of carcinogenicity for **Metallic Nickel** observed in human studies

Classifications & Labels in the EU

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Endpoint	Nickel Sulfate	Nickel Chloride	Nickel Nitrate	Nickel Carbonate	Nickel Hydroxide	Nickel Sub & Sulphide	Nickel Mon-Di- & Tri-oxide	Metallic Nickel
Physical Properties	None	None	O;R8	None	None	None	None	None
Acute Oral	Xn;R22	T;R25	Xn;R22	Xn;R22	Xn;R22	None	None	None
Acute Inhalation	Xn;R20	T;R23	Xn;R20	Xn;R20	Xn;R20	None	None	None
Dermal Irritation	Xi;R38	Xi;R38	Xi;R38	Xi;R38	Xi;R38	None	None	None
Eye irritation	None	None	Xi;R41	None	None	None	None	None
Dermal Sensitization	R43*	R43*	R43*	R43	R43	R43	R43	R43**
Respiratory Sensitization	R42	R42	R42	R42	R42	None	None	None
Chronic Toxicity	T; R48/23	T; R48/23	T; R48/23	T; R48/23	T; R48/23	T; R48/23	T; R48/23	T; R48/23
Reproductive Toxicity	Cat2;R61	Cat2;R61	Cat2;R61	Cat2;R61	Cat2;R61	None	None	None
Mutagenicity	Cat 3;R68	Cat 3;R68	Cat 3;R68	Cat 3;R68	Cat 3;R68	Cat 3;R68	None	None
Carcinogenicity	Cat 1; R49	Cat 1; R49	Cat 1; R49	Cat 1;R49	Cat 1;R49	Cat 1; R49	Cat 1; R49	Cat 3; R40
S-Phrases	53, 45, 60, 61	53, 45, 60, 61	53, 45, 60, 61	53, 45, 60, 61	53, 45, 60, 61	53, 45, 60, 61	53, 45, 61	(2), 36, 37, 45

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Non-cancer Respiratory Toxicity

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Respiratory (non cancer) Effects: Do they happen in Humans and at what levels?

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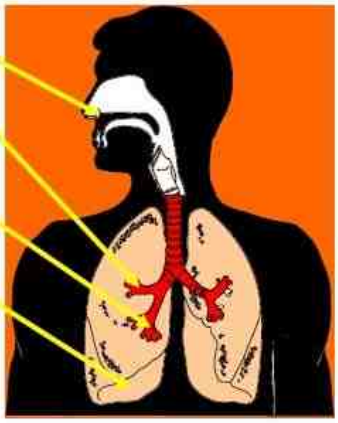
- "Immunotoxicity" (e.g., allergies)
  - Asthma
- Bronchial disease (e.g., bronchitis)
  - Mucus
  - Stiff lungs
- Deep lung disease and infiltrative disease
  - Acute pneumonia
  - Lung Inflammation
  - Lung fibrosis



Respiratory (non cancer) Effects: Why is it important to get it right?

NIPERA

- To protect the workforce and public from risks associated with exposure to nickel compounds
- To assure that proper Classifications are assigned to the various forms of nickel and health risks are not missallocated

Nickel Toxicity – Non-Cancer Respiratory Effects

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- Asthma
  - There is evidence of asthma associated with soluble nickel exposures among platers.
  - Case reports of asthma associated with nickel metal exposure exist but data are far from definitive.
  - Occupational physicians do not see an increased incidence of asthma among nickel refinery workers

Nickel Toxicity – Non-Cancer Respiratory Effects

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- Chronic Bronchitis, Nasal Irritation
  - This is an important datagap.
  - The nickel producing industry ran a study of respiratory symptoms among nickel refinery workers.
  - 12 company/sites participated in the study.
  - Workers completed a simple questionnaire of respiratory symptoms, complemented with lung function data and X-ray information when available.
  - Data were submitted to researchers for collation and analysis

Nickel Toxicity – Non-Cancer Respiratory Effects

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- Fibrosis
  - Human study demonstrates X-ray abnormalities associated with cumulative exposure to soluble and sulphidic Ni (Berge & Skyberg 2003). Thresholds:
    - Soluble: 0.013 mg Ni/m^3 (inhalable)
    - Sulphidic: 0.0005 mg Ni/m^3 (inhalable)
  - Animal studies demonstrate fibrosis at histological level after prolonged exposures to soluble Ni (NTP study), sulphidic Ni (NTP study), and Ni metal (recent 90-day study). Thresholds:
    - Soluble: 0.03 mg Ni/m^3 (MMAD 2 µm)
    - Sulphidic: < 0.1 mg Ni/m^3 (MMAD 2 µm)
    - Metal: 1 mg Ni/m^3 (MMAD 2 µm)

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Nickel Toxicity – Sensitization/Dermatitis

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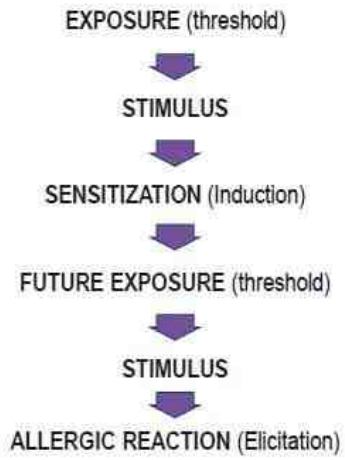
Nickel Toxicity – Sensitization/Dermatitis

- Two phases of nickel allergy:
  - Induction - results in nickel **sensitization (allergy)**
    - Initiation of immune system reaction
    - Threshold reaction (higher dose needed than for elicitation)
    - ~2 weeks to develop immune system reaction
  - Elicitation - results in nickel **dermatitis**
    - Allergic response in nickel-sensitized individuals
    - Threshold reaction (lower dose than for induction)
    - Within 24-48 hours of exposure dermatitis appears



Nickel Toxicity – Sensitization/Dermatitis

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- Nickel dermatitis is an allergic reaction to nickel ions in nickel-sensitized (allergic) individuals
- The most common source of induction of nickel allergy in the general public is **skin piercing** and subsequent exposure to nickel-releasing jewelry
  - Piercing eliminates the skin barrier
- The most common elicitation source in the general public is **direct and prolonged dermal contact with nickel-releasing materials (e.g. jewelry, watches)**

Nickel Toxicity – Sensitization/Dermatitis

- Nielsen, 1999 tested patients with a current flare-up of dermatitis to determine whether nickel treatment worsened their condition
- Data from this study suggests that for this worst case scenario 0.012 mg Ni/kg/day could still be a marginal LOAEL for exacerbating nickel dermatitis in sensitized individuals
- Currently a human study is underway to determine how long exposure must occur to elicit a reaction in a sensitized individual

Reproductive Toxicity

Epidemiological Reproductive Studies

NiPERA

- Animal studies have shown that significant oral exposure to solubilized nickel during the later stages of pregnancy in rats can cause "perinatal lethality"
- To determine whether nickel could cause reproductive effects in humans NiPERA sponsored an epidemiological study of reproductive effects in women exposed to relatively high soluble nickel levels in the Kola Peninsula nickel refinery

Human Reproductive Epidemiology (1998-2008)

- NiPERA provided support and expert guidance to researchers

- Key study showing very low RIS
  nickel in humans
- NiPERA animal study set No Eff

Epidemiological Reproductive Studies

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- These studies demonstrate that while a reproductive "hazard" can be demonstrated in animals, there is no demonstrable "risk" of reproductive impairment in humans!
- A weight of evidence approach to the future re-evaluation of reproductive toxicity of nickel substances will be needed!

Nickel Toxicity – Reproductive Effects

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- Workers and the general public are not at risk from the reproductive toxicity effects reported in animal studies because the level at which effects were seen in the studies is approximately :
  - 100 times higher than the WHO 2005 nickel TDI of 12 µg Ni/kg/day
  - 400 times higher than the normal total oral dose to nickel from food, drinking water and other sources.
- There is no reliable evidence of any other reproductive effects on men or women.

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Environmental Research

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Ni in the Environment

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- Major Sources of Ni
  - Ni operations
  - Fossil Fuel combustion
  - Fertilizer, agricultural sludge
  - Products in commerce are relatively minor sources!

- Known effects of Ni
  - In the natural environment: Plant toxicity
  - In the laboratory: Plant, fish, bird, invertebrates...

Goal: Place environmental exposures and environmental effects into a reasonable and science-based context

Drivers for Ni Environmental Research

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- Stewardship (Helping Member Companies):
  - Fulfill compliance obligations
  - Understand environmental consequences of operations and products

- Legislation
  - Ensure that Global Environmental Quality legislation is reasonable and based on sound science

Environmental Compartments

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- Freshwater

  - Many sources of Nickel to FW
  - Economically important

- Marine

  - Many Nickel operations located on coasts
  - Shipping cargo via marine waters
  - Economically important

- Sediment

  - Sediments may act as "sink" or "source"

- Soil

  - Important for agriculture
  - Soils receive Ni from air, fertilizer, sludge

Nickel in the Environment: Why is it important to get it right?

NiPERA

- Nickel Environmental Quality Standards (EQS) under the EU Water Framework Directive (WFD)
  - Ni EQS value affects company discharge permits and operating conditions

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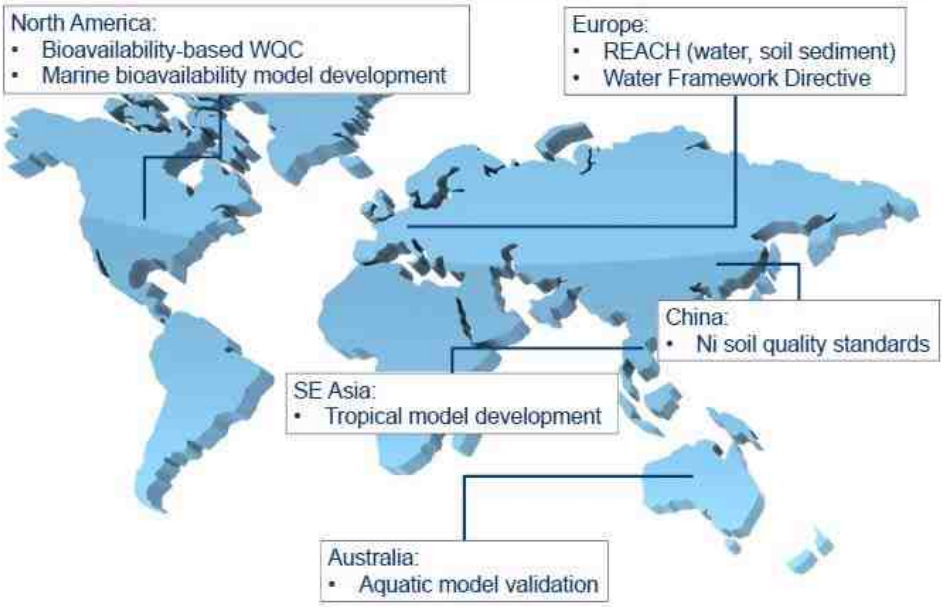
NiPERA's bioavailability research: A global initiative

NiPERA



Research Area: Nickel in the Environment

NIPERA

- Regulatory requirement: Review/ Revision of EQS for Priority Substances required every 4 years.
- Previous EQS value was based on drinking water.
  - EQS value must be protective of ALL freshwater bodies in EU (could be overly conservative)
  - Opposition from Denmark on reduction of AF
  - Bioavailability not accepted into EU regulation

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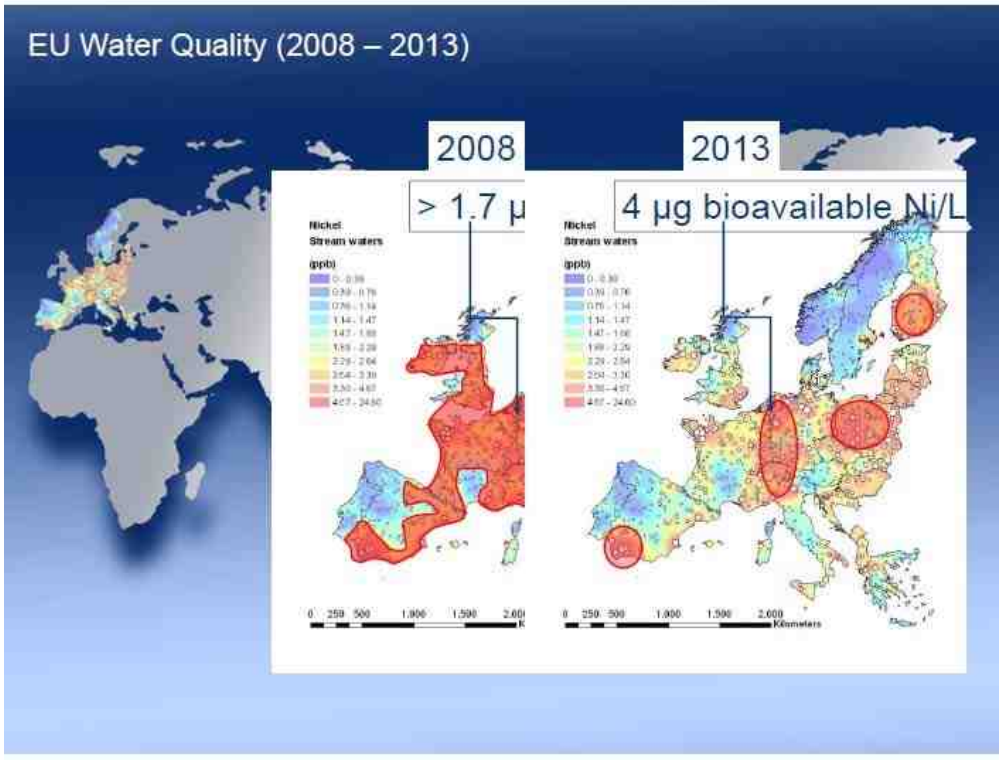

Research Area: Nickel in the Environment

NiPERA

- Current Status:
  - Success! Due to NiPERA's input the EU Commission proposal supported the NiPERA position for a bioavailable Ni EQS of 4ug/L.
  - EU Council and Parliament to vote in May or June.
  - First time bioavailability accepted in EU regulation.

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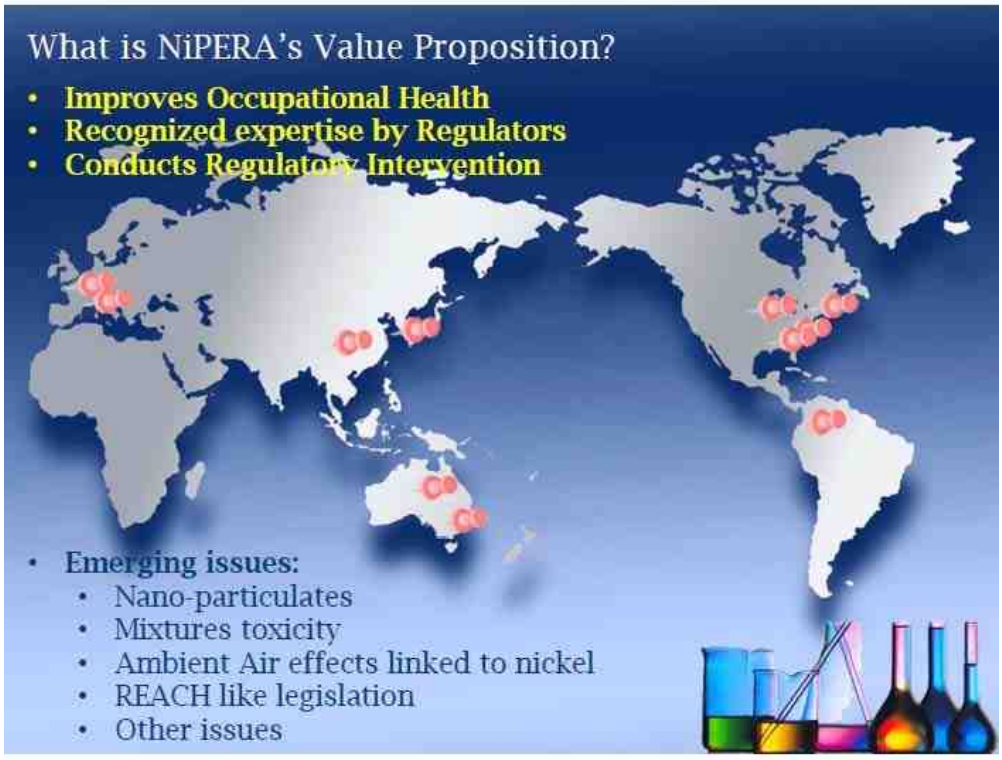

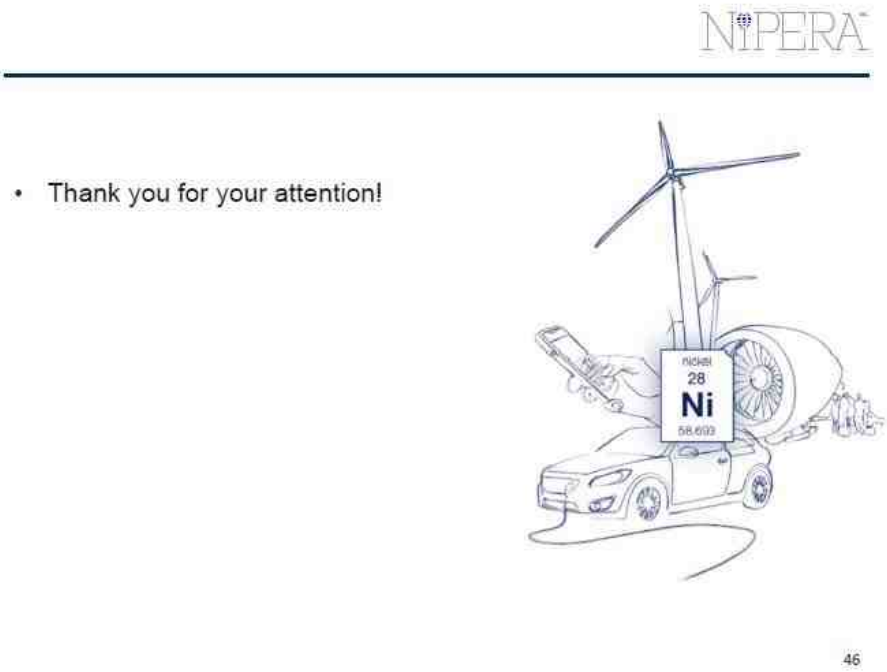

About the author

The NASF Scientific Achievement Award is the Association's most prestigious award. Its purpose is to recognize those whose outstanding scientific contributions have advanced the theory and practice of electroplating, metal finishing and allied arts; have raised the quality of products and processes; or have advanced the dignity and status of the profession.

Dr. Hudson Bates has more than 30 years of experience in toxicology, with specialization in developmental toxicology, reproductive toxicology, and neurotoxicology. During more than the past two decades, this specialized knowledge has been applied to the study of the toxicology of nickel and its compounds.

Dr. Bates received his Ph.D. in toxicology from the University of Arkansas for Medical Sciences, his M.S. in toxicology from the Albany Medical College of Union University, and his B.S. in biology from the State University of New York at Albany. Dr. Bates became a Diplomat of the American Board of Toxicology (D.A.B.T.) in 1992 and has successfully completed the recertification testing in 1997, 2002, 2007, 2012, and 2017. Dr. Bates has also had specialty training in advanced behavioral and neurophysiological testing methods for neurotoxicants.

Dr. Bates has been employed by the Nickel Producers Environmental Research Association (NiPERA) since 1994 and is currently the Executive Director of the organization. He is responsible for guiding the research and communication activities of five doctoral level scientific staff and for guiding the strategic research direction of NiPERA. Dr. Bates has maintained a high level of personal scientific interaction guiding research programs and addressing regulatory issues on human and environmental toxicology.

In previous positions, Dr. Bates directed and/or managed toxicology laboratories at the U.S. FDA's National Center for Toxicological Research (NCTR), Research Triangle Institute (RTI), and Transgenic Sciences, Inc. His experience includes numerous interactions with regulatory authorities, contact with various industries on scientific issues related to their commodities, extensive public speaking experience, and some product litigation defense experience.