



CASF Conference

Nickel Developments: Research and Risk Update

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1. Review of Recent Issues
 2. Details of Nickel Metal Reproductive Classification
 3. Potential Challenges to Ni Environmental Quality Standard (EQS) under the EU Water Framework Directive (WFD)
 4. Activity within Canada on Ni Water Quality Guideline (WQG)
 5. US EPA regional focus on bioavailability-based Water Quality Criterion (WQC) for Ni

Why is NiPERA involved?

- To defend appropriate science based regulations!
- To provide up to date world class research to influence classification and risk assessment decisions!
- To support nickel production while protecting worker health!
- To support public health from exposure to nickel in the marketplace!



To protect industry's license to "operate and market"!

Classification:

- NiPERA scientists managed to ensure that nickel and nickel compounds received the lowest priority in California for reprotoxicity hazard assessment. **UPDATE!**

Water quality standards:

- The U.S. EPA invited NiPERA scientists to participate in discussions to revise the Ni ambient water quality criteria leverage the success with the EU EQS!
- NiPERA scientists met with Env Canada staff to discuss metal risk assessment approaches which was received with great interest.

Sediment:

- ECHA invited NiPERA scientists to participate in the Partner Expert Group (PEG) that will be involved in revising ECHA's environmental risk assessment guidance for the sediment compartment.

REACH:

- On-time submission of the 6th annual update of the EU dossiers.

Nickel Tropical Risk Assessment Research Program:

- Excellent progress has been made in the development of a model of considering effects of nickel exposure to the Tropical Environment (e.g., coral reefs and mangrove swamps). Laboratory work will continue in 2017-18.

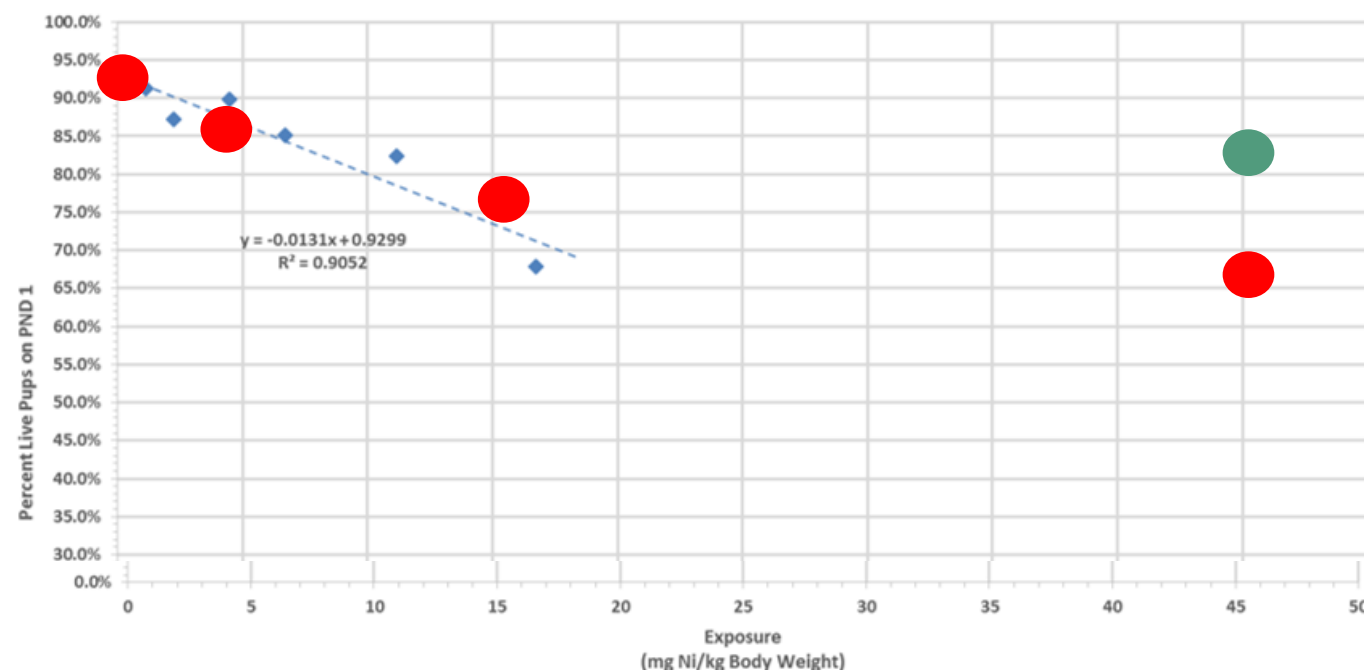
Risk Assessments:

- Australian Authorities have requested a series of meetings and comments from NiPERA scientists in their IMAP risk assessments of nickel.
- EPA IRIS Risk Assessment back on the priorities list!

Metallic Nickel Reproductive Classification

Nickel nanoparticles exposure and reproductive toxicity in healthy adult rats. Kong L., Tang M., Zhang T., Wang D., Hu K., Lu W., Wei C., Liang G. and Pu Y. Int J Mol Sci. 2014;15(11):21253-69.

- A one-generation reproductive study indicating that oral exposure to nickel metal **nanoparticles** at relatively high levels is able to replicate the kind of reproductive effects that have been seen before with water soluble nickel compounds
- One group of animals exposed to **micron**-size particles of nickel metal also experienced a similar type of response



Reproductive Toxicity of Metallic Nickel

Nano-forms: the results from the Kong et al. study are consistent with the positive animal data for soluble nickel compounds. Unclear relevance of negative epidemiological data for nanos. Lack of mode of action information to demonstrate non-relevance of effects to humans

Category 1B

Micron-size forms: Kong et al. study provides suggestive evidence of an association between high oral exposure to micron-size powders and adverse reproductive effects. Existing toxicokinetic study indicated 100-fold lower oral absorption than soluble nickel



Massive forms: oral toxicokinetic study (1 mm pellets) indicated that at the highest possible dose, the blood nickel levels achieved did not exceed (although they were close to) the Ni sulphate threshold for reproductive effects

No classification

Possible Studies with μ -size Nickel Metal

Study	Information provided	Implications for hazard assessment	Length (months)	Cost (USD)
Toxicokinetics	Compare absorbed doses to assess if threshold for reproductive effects can be exceeded	If threshold by one route is exceeded, a Category 1B classification is justified. If threshold by one route is not exceeded, it would support a Category 2 classification but not enough to declassify. A reproductive study would still be needed to scientifically justify No classification	3-6	350k
Prenatal Developmental (PNDT)	Examines prenatal and fetal exposure only <ul style="list-style-type: none"> Maternal toxicity Teratogenesis 	Makes sense only when there is no information on possible types of developmental effects. If one or two gen studies with Ni metal are negative, a second species PNDT may be desired to rule out all forms of developmental toxicity (e.g., birth defects)	6	200k
Extended one-generation (EOGRT)	Examines prenatal, fetal, & lactation exposure (F1). Optional: extend F1 exposure through mating cycle (F2): <ul style="list-style-type: none"> Maternal and paternal toxicity Fertility Perinatal mortality Lactation <u>Optional</u>: Amplification of toxicity in F2 	Definitive study for perinatal mortality <ol style="list-style-type: none"> If study is positive, a Category 1B is justified. If core study is negative, an F2 extension may be desired (to obtain robust negative results). If F1 & F2 study is negative, No classification warranted. If F1 & F2 study is negative, a PNDT-rabbits may be desired to completely rule out birth defects. 	12 (+6)	550k (+150k)
Two-generation	Examines pre-mating, mating, pregnancy, lactation (F0); fetal, lactation, maturation, pre-mating, mating, pregnancy exposure (F1); fetal, lactation exposure (F2) <ul style="list-style-type: none"> Maternal & paternal toxicity Fertility Lactation Perinatal mortality Amplification of toxicity in F2 generation 	Definitive study for perinatal mortality. <ol style="list-style-type: none"> If study is positive, a Category 1B is justified. If study is negative, No classification warranted If study is negative, a PNDT in rabbits may be desired to completely rule out teratology effects 	18 (+6)	550k (+150k)

- Applicable standard information requirements for reproductive toxicity under REACH:

Standard information requirement	Need to provide further data	
EOGRTS	(+)	(in particular in light of Kong et al.)
PNDT (1st species)	(-)	(fulfilled by read-across from a Ni compound)
PNDT (2nd species)	(?)	(arguably fulfilled by a Weight of Evidence argument – uncertain whether it would be accepted by ECHA)

- Obligation to submit testing proposal(s) before testing:
 - Opportunity to get regulatory approval for the proposed approach
 - Testing proposal process is cooperative (contrary to compliance checks)
 - Appropriate ‘interim’ classification should be included in the dossier

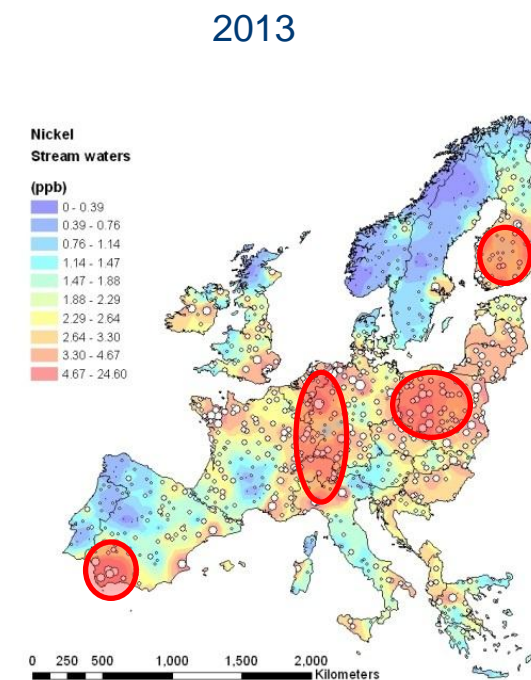
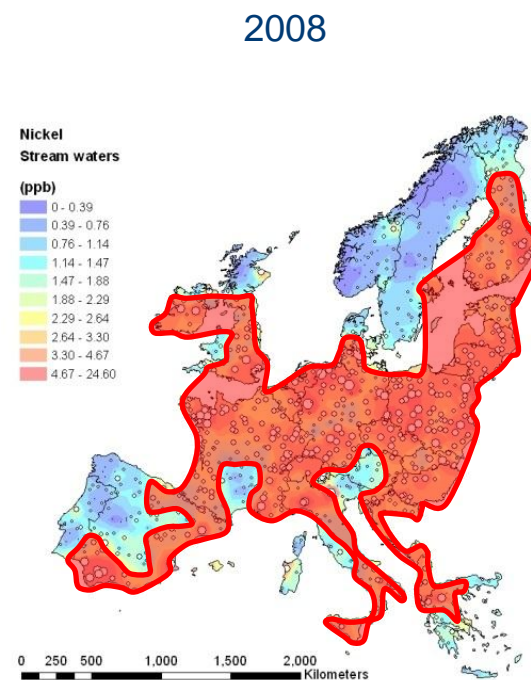
- In view of Kong et al. study with nickel metal nano powders and the lack of robust data for micron-size powders of nickel metal, **further animal testing of the micron-size powders is recommended**
- Of the various study options that would produce robust and clear data on the reproductive developmental hazard of micron-size nickel metal, **an extended one generation study (EOGRTS) is preferred.**
- It is recommended that a **testing proposal for an EOGRTS** be submitted to ECHA (via the Ni Consortia). (A **conditional testing proposal for a PNDT 2nd species** can be included)
- Shorter or less costly studies would not provide sufficiently convincing data for **No Classification** and would result in further testing

While further animal testing is being conducted, self-classifying nickel metal (micron-size powders) as a Category 2 reproductive toxicant

Environmental Quality Standards for Water

Background

- 2013: Ni EQS of **4 µg bioavailable Ni/L** established by EU (1.7 µg Ni/L originally proposed)
 - Reflected state of science
 - Bioavailability-based (may be at least 40 µg Ni/L for some waters)
 - Assessment Factor = 1



License to operate issue – potential impacts for effluent release!



What is the issue?

- EU preparatory activities for next revision EQS Directive (2020):
 - Late 2015: NL requested review of Ni EQS
 - Dutch bioavailability models (PNECPro): EQS < 4 µg Ni/L for certain water chemistries
 - Dutch position: AF should be increased to at least 2

In parallel:

- Commission and Chemicals WG are revising approaches for deriving bioavailability-based EQS for metals as part of the Zn prioritization process
- Reference EQS for Ni (currently 4 µg/L) could be affected



What could be the impact of increasing the AF?

- Halve the reference Ni EQS (from 4 $\mu\text{g Ni/L}$ to 2 μg)
- Reduce allowable Ni concentrations in discharges by at least 2-fold
- Increase compliance failures and costs for industry



- NI is currently working with MS that are implementing bioavailability-based EQS using other models (such as bio-met and M-BAT): FR, UK, SE, FI & others
- A critical analysis of PNEC-Pro was conducted and the paper was accepted for publication in Environmental Toxicology & Chemistry
- The NI will work to reassure EC that bioaccessibility-based Ni EQS using AF of 1 is scientifically robust:
 - Highlight additional scientific information that supports AF of 1 in Position Paper

Outlook: Current EC focused on identifying new Priority Substances

Background

- Canadian Council of Ministers of the Environment (CCME)
 - Update of 1995 Ni WQG
 - Current WQG is based on old ecotoxicity data and old views on bioavailability (only water hardness considered)

What is the issue?

- CCME considering use of Alternative Water Quality Parameter Assessment approach
 - “borrow” approach from EU for Ni EQS under WFD
 - Tailor derivation to meet specific Canadian requirements

License to operate issue

What is the impact?

- In theory, Canadian provinces/territories are not obliged to use CCME WQGs.... in practice, most do!
- CCME WQG will inform Federal Policy on Ni, and may form basis of future mining effluent limits

What are we doing about the situation?

- Briefing of Canadian NI Member Company representatives
 - Consensus: Recognition of the EU EQS approach would be favorable outcome

Next steps

- Engagement with CCME representatives through Mining Association of Canada
- If feasible, further engagement with favorable CCME representatives on the scientific depth and practicality of the EU EQS approach
- Behind the scenes work with our network on early drafts of the Ni WQG dossier



Background

- US EPA Region 5: actively considering development of bioavailability-based WQC for Ni (and Zn)



What is the issue?

- Current hardness-based approach (from 1986) shows exceedances where full bioavailability normalization suggests no risk
- If implemented by Region 5, bioavailability-based WQC could be adopted at Federal level (all states would be obliged to meet this WQC)



What are we doing?

- NiPERA is working with US EPA Region 5 and other stakeholders with the goal of achieving:
 - Integration of current Ni bioavailability modeling into formats acceptable to US EPA
 - Testing of bioavailability relationships in waters of extreme chemistry (high hardness/high pH/low DOC and low hardness/low pH/high DOC)

- Regulatory authorities appear to be (re)turning their attention to metals during this time period
 - IARC Welding
 - EFSA TDI
 - WHO Drinking Water
 - EPA IRIS update
 - EPA EQS
 - Oregon and Michigan Air Standards
 - Canadian Air Standards
 - Canadian EQS
 - Australian IMAP
 - Korea REACH
 - *etc.*
- Whenever this occurs, the inevitable result is a tightening of regulatory standards