



2018 ANNUAL REPORT

COVERING ACTIVITIES FROM
JANUARY 1, 2018 – DECEMBER 31, 2018
AND BUDGETARY INFORMATION FOR FISCAL YEAR 2018



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Introduction

NiPERA Inc., the science division of the Nickel Institute, sponsors scientific research related to nickel, synthesizes data and results, and communicates research outcomes to wide ranges of audiences and stakeholders. In 2018, these activities supported the Nickel Institute's mission to promote the use of nickel in appropriate applications and the setting of regulations based on science. The 2018 Business Plan was delivered, within budget.

Leading NiPERA's science team for part of this year made me realize the depth and the breadth of the staff's expertise and commitment to excellence. Anticipating and responding to regulatory initiatives as well as delivering robust research positions establishes NiPERA as a credible partner worldwide. Whether advising a member company or meeting with regulatory authorities, we rely on robust and peer-reviewed research results to promote science-based decisions.

Dr. Adriana Oller
Executive Director, NiPERA Inc.

Science Highlights

Reprotoxic listing of soluble nickel compounds in USA

California Office of Environmental Health Hazard Assessment (OEHHA) considered the appropriate listing of nickel substances as reproductive toxicants at their October 2018 meeting. NiPERA, together with scientists from Gradient and Exponent responded to the public consultation submitting detailed comments on the need to limit the listing to certain endpoints (developmental effects) and substances (soluble nickel compounds) based on the strength of the animal and human evidence. The Developmental and Reproductive Toxicant Identification Committee concluded that soluble nickel compounds, but not insoluble compounds or nickel metal, needed to be listed under Prop65 as developmental and male reproductive toxicants. OEHHA is currently working on defining the meaning of "soluble nickel compounds" and setting safe harbor levels for these compounds.

Cobalt metal classification Carco 1B, all routes

Cobalt metal is an animal carcinogen based on the 2014 U. S. National Toxicology Program studies via inhalation that demonstrated increased lung tumors among exposed animals. Because typically, nickel metal and nickel-containing stainless steels contain more than 0.01% cobalt, NiPERA worked with the Cobalt Institute (CI) to review the European Union (EU) methodology used to assign potency to carcinogenic substances. This methodology resulted in cobalt metal being assigned a high potency ranking and associated very low concentration limit in mixtures (e.g., alloys). We identified several concerns, including the applicability of a database based on oral carcinogenicity studies with organic substances to assess potency of inorganic metal substances after inhalation. ECHA is now convening an expert group to review this approach.

Since there is no oral carcinogenicity study, it is not possible to completely rule out an "all routes" animal carcinogenicity hazard for cobalt metal. Both initiatives (low concentration limit and all routes carcinogen classification) can have profound effects on nickel markets as they affect the classification (based on bulk concentration of Co metal) of some nickel metal grades and stainless steels. Therefore, it is important to consider data gaps and how they can be filled in with robust scientific data to back up any regulatory decisions.

Use of bioelution to refine the classification of alloys

NiPERA has been actively involved in the EU discussions regarding the regulatory acceptability of bioelution-based approaches for a variety of applications. Regulatory authorities have been hesitant to accept bioelution data-based assessments due to the lack of a validated and internationally recognized test protocol (e.g., Organization for Economic Co-operation and Development, OECD test guideline). A bioelution protocol for a gastric test was submitted by the metal commodities lead by Eurometaux and NiPERA to the European Centre for the Validation of Alternative Methods (ECVAM) for validation. Two main applications of the protocol were included: for grouping and read across of metal-containing substances and for refinement of alloy classification. The metals industry also moved closer to defining a consistent bioelution-based approach for the classification of alloys that includes safety nets to cover alloys in which matrix effects result in higher metal ion releases than predicted by content. This is of utmost importance in view of the impact that the proposed cobalt metal classifications can have on alloys.

Nickel OELs proposed in EU

In March 2017, the European Commission gave a mandate to the European Chemicals Agency (ECHA) Risk Assessment Committee (RAC) to derive science-based Occupational Exposure Limits (OEL) for nickel and nickel compounds. As one of the stakeholders in this process, NiPERA shared published manuscripts and final research reports with ECHA. The studies provided scientific support for a mode of action-based threshold for cancer and addressed occupational exposure sampling issues. Comments were also provided by NiPERA during the public consultation period. In March 2018, the RAC opinion recommended an inhalable OEL of 0.03 mg Ni/m³ for nickel compounds and a respirable OEL of 0.005 mg Ni/m³ for nickel metal and nickel compounds. The OEL setting process for nickel compounds under the Carcinogen, Mutagen Directive continued with the undertaking of a socio-economic cost-benefit assessment by DG Employment. NiPERA and the Nickel Institute (NI) have been actively facilitating a survey of EU companies and providing information to consultants as needed. The next discussions are expected to take place at the 2019 Advisory Committee on Safety and Health at work (ACSH), a tripartite group with representation from government, employers and workers. The setting of an OEL for nickel metal is expected to be considered later under the Chemical Agents Directive. EU OELs can set precedents for other parts of the world.

Update on REACH and Korea REACH

The NiPERA-NI team working on REACH (Registration, Evaluation, Authorization and Restriction of Chemicals) legislation updated dossiers for 13 nickel substances. The updates include newly published studies, read across tables in new ECHA format, and new uses. This ensures that Nickel Consortia Member Companies remain in compliance and able to continue their market access in the EU. Nickel's approach is best practice by industry standards and well regarded by ECHA. The REACH team participated in the Metals and Inorganics Sectorial Approach (MISA) workshop (industry and ECHA initiative) aimed to improve the quality of the dossiers and prepared a MISA workplan to integrate the learnings from the workshop in future dossier updates.

In vitro mutagenicity testing of nickel metal powder in mammalian cells was conducted to fill in REACH data requirements. The in vitro gene mutation study was negative while the study of chromosomal effects showed interference by insoluble nickel metal particles and will be repeated next year.

NiPERA continued to support nickel compounds' registrants in Korea to assure that the most robust studies are used in those registrations.

Nickel nanoparticulate research program progresses

A new acute toxicity study was initiated in 2018 and progress was made on several ongoing projects (phys-chem analyses, bioelution analyses, as well as human health toxicity and environmental toxicity reports). All projects are expected to be completed on or before Q1 2019. This program proactively addresses current toxicological data gaps and risk characterization issues specific to nanoforms of nickel metal and compounds that have the potential to differentially impact human and environmental health regulations.

Developments on nickel allergic contact dermatitis

The discussion on ECHA's restriction of articles intended to come into direct and prolonged contact with the skin continued in 2018. NI-NiPERA submitted comments on the draft list of articles and published the results of the Phase 1 and 2 definition of prolonged contact studies. These studies demonstrate that ECHA's definition of "prolonged contact" is overly precautionary. In early 2019 a dermatitis expert workshop will be organized to review the state of the science and make sure that datagaps are addressed in the next phase of the NiPERA study.

NiPERA's Kate Heim co-authored a book chapter in a 2018 published book entitled "Metal Allergy: From Dermatitis to Implant and Device Failure" (2018. Editors: Chen, Jennifer K, Thyssen, Jacob P.; Springer International Publishing; <https://www.springer.com/gp/book/9783319585024>). This book provides a comprehensive overview of the use and regulation of metals in our society, metal properties, and available testing methodologies and is likely to serve as a reference for a variety of audiences interested in metal allergy. In addition, three videos were recorded in which "Dr. Kate" provides information on nickel allergy and nickel allergic contact dermatitis. These videos were created in cooperation with the NI Communications division as part of their public outreach effort. The videos are available to the public via YouTube at:

[Nickel allergy: What you need to know](#)

[Nickel allergy and ear piercings](#)

[Nickel allergy – nickel allergic reactions](#)

Gains made on environmental quality standards for nickel

In 2018, NiPERA led a series of initiatives around the world to ensure that nickel Environmental Quality Standards (EQS) and environmental classifications for nickel and nickel substances reflect the latest scientific information.

- **EU:** NiPERA continued its dialogue with the European Commission on the proposed revision of the nickel EQS under the Water Framework Directive, which has been requested by the Netherlands since 2015. NiPERA provided comments on a provisional revision to the nickel EQS prepared by the Commission's Joint Research Centre. Later in the year, the Commission announced that no revision to existing EQS would be made until 2020 at the earliest. This means that Member States can focus on implementing the current bioavailability-based EQS.

NiPERA was part of the Eurometaux delegation participating in a Commission task force that developed guidance for implementing bioavailability-based EQSs for metals. NiPERA's participation allowed for the Commission's official guidance to reflect the state of the science in terms of selecting appropriate bioavailability models, including bioavailability in the compliance checking process, and accounting for natural background concentrations of metals when checking compliance.

- **North America:** NiPERA led efforts to publish the outcomes of a 2017 Society for Environmental Toxicology and Chemistry (SETAC) workshop *Bioavailability-based Aquatic Toxicity Models for Metals*, co-sponsored by the United States Environmental Protection Agency (US EPA) and co-chaired by NiPERA's Chris Schlekot. In 2019, a series of six manuscripts will be submitted for publication in the journal *Environmental Toxicology and Chemistry*.

Publication of the SETAC workshop findings is an important step in US EPA's efforts to revise existing Water Quality Criteria (WQC) for metals using state of the science approaches that include bioavailability modelling. NiPERA continued working with US EPA through a Cooperative Research and Development Agreement that was established in 2017. Progress was made on approaches for selecting reliable and relevant ecotoxicity data and identifying appropriate bioavailability modelling approaches. In parallel, the NiPERA-sponsored research examining the relevance of nickel bioavailability models for US waters with unique water chemistry compositions was completed in 2018 by the United States Geological Survey; this work will contribute to the technical basis for establishing a revised nickel WQC by the US EPA.

- **China:** NiPERA sponsored a workshop on metal bioavailability in conjunction with the Chinese Research Academy of Environmental Science (CRAES) in September 2018. The Beijing workshop provided an opportunity for NiPERA to describe the process by which bioavailability-based standards for nickel and other metals can be developed in China and it resulted in a joint workplan for 2019. The proposal to validate existing nickel bioavailability models in Chinese waters will support China's goals of revising existing standards for nickel by 2020.
- **Japan:** NiPERA initiated a study with the National Institute of Advanced Industrial Science and Technology to validate existing nickel bioavailability models in Japanese waters. Preliminary results of this work showed promise in terms of delivering data that would provide an alternative to the EQS proposed by the National Institute of Environmental Studies, which is precautionary in nature.
- **Australia:** Work began to determine a bioavailability-based Water Quality Guideline (WQG) for nickel following recently revised Australia-New Zealand guidance. This work is being performed in conjunction with the Australian Committee for WQG and is expected to be completed in 2019.

Tropical risk assessment near completion

The experimental and data gathering components of NiPERA's tropical environmental risk assessment research program were completed in 2018. Advances in understanding the effects of nickel to tropical ecosystems such as coral reefs, freshwater systems, and benthic communities will be communicated to relevant stakeholders in early 2019. In general, the outcome of NiPERA's research shows that tropical ecosystems are within the same sensitivity range to nickel exposure as temperate ecosystems, which allows the use of the extensive temperate ecotoxicity databases for tropical risk assessments. This research also allowed NiPERA to learn of an effort within New Caledonia to revise this island nation's nickel EQS and created an opportunity to collaborate on this initiative in 2019.

New test methodology for environmental hazard classification of nickel

NiPERA coordinated a multi-metallic initiative to develop a new test methodology and a Weight of Evidence approach to assess the environmental hazard category of rapid degradability. Since 'degradability' is not a relevant criterion for metals, the concept of rapid removal from the water column was developed as an analogous category that is suitable for determining appropriate environmental classification of metals and metal substances. The extended Transformation/Dissolution test methodology and supporting research were shared with ECHA, the European Commission, and the OECD in 2018. The comprehensive data package demonstrates the scientific validity of the tool for assessing rapid removal of metal from the water column. If accepted, the approach will provide a refinement to the existing environmental classification framework for metals and metal compounds.

2018 Peer Reviewed NiPERA Manuscripts

Publication of NiPERA-sponsored research in the peer-reviewed scientific literature is a key factor in the dissemination of research results. These publications are key resources in ensuring that scientific and regulatory experts have access to the best scientific evidence possible when conducting risk assessments on nickel and its compounds.

Heim K, Basketter D. 2018. Chapter 5. Metal Exposure Regulations and Their Effect on Allergy Prevention. In *Metal Allergy: From Dermatitis to Implant and Device Failure*. Editors: Chen JK and Thyssen JP. Springer International Publishing. pp. 39-54.

Nixon RL, Higgins CL, Maor D, Rajgopal Bala H, Lalji A, Heim KE. 2018. Does clinical testing support the current guidance definition of prolonged contact for nickel allergy? *Contact Dermatitis* 79(6):356-364.

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Lombaert N, Mackie C, Verougstraete V, Brouwers T, Van Assche F, Oller A. 2018. Use of bioelution as a screening tool for characterization of substances. *Am J Analytical Chemistry* 9:134-149.

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Nys C, Van Regentmortel T, De Schamphelaere K. 2018. The effects of nickel on the structure and functioning of a freshwater plankton community: a microcosm experiment. *Environmental Toxicology and Chemistry* [Accepted pending revisions].

Gissi F, Stauber JL, Binet MT, Trenfield MA, Van Dam JW, Jolley DF. 2018. Assessing the chronic toxicity of nickel to a tropical marine gastropod and two crustaceans. *Ecotoxicology and Environmental Safety* 159:284-292.

Budget

The NiPERA budget reporting paradigms are based upon Generally Accepted Accounting Principles (GAAP) for Not-for-Profit [501(c)(3)] organizations in the United States where NiPERA is incorporated. Consequently, budgetary liabilities are recorded in full when they occur which offers the best method of managing expenses, albeit with some impact on cash flow management. NiPERA continues to utilize monthly “just-in-time” dues payments from the Nickel Institute which avoids the banking of large sums of money by NiPERA for projects while awaiting invoicing. This is critical as project invoices are often received by NiPERA after the liability for a project is recorded to the budget and often after the deliverables for a project are received by NiPERA staff.

Table 1: NiPERA's 2018 Operating Expenses

Description	Total USD
Revenue	
Nickel Institute Dues	\$3,102,836
Cost Recovery Revenue	75,000
Total Revenue	3,177,836
Operating Expenses	
Labor & Fringe	165,617
Administrative Expenses	66,612
Travel	59,056
Research - Nickel Metal	35,429
Research - Nickel Alloys	58,700
Research - Occupational Exposure Limits	39,044
Research - Environmental Quality Studies	319,425
Research - Emerging Issues	(3,022)
Research - Nanoparticulates	72,029
Research - Nickel Allergy Contact Dermatitis	26,216
Research - Program Support	138,109
Project Travel	112,056
Project Salary & Benefit	1,256,939
Project Office Costs	107,765
Transfer Costs	896,992
Realized Loss / (Gain) on Foreign Exchange	5,210
Depreciation Expense	62,540
Total Operating Expenses	3,418,717
Operating Income	(240,881)



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