



2017 ANNUAL REPORT

COVERING ACTIVITIES FROM
JANUARY 1, 2017 – DECEMBER 31, 2017
AND BUDGETARY INFORMATION FOR FISCAL YEAR 2017



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Introduction

NiPERA Inc, the science division of the Nickel institute, sponsors scientific research, synthesizes data and results, and communicates research outcomes to wide ranges of audiences and stakeholders. In 2017, 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 2017 Business Plan was delivered, within budget.

"Our peer-reviewed research provides strong evidence and a solid foundation for science-based decision making in jurisdictions across the world."

Dr. Hudson Bates
Executive Director, NiPERA Inc.

Science Highlights

EU OELs

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 Limit (OEL) for nickel and nickel compounds. As one of the stakeholders in this process, NiPERA shared published manuscripts and/or 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 December 2017, the RAC draft opinion recommended an inhalable OEL of 0.03 mg Ni/m³ for Ni compounds and a respirable OEL of 0.005 mg Ni/m³ for nickel metal and nickel compounds. The RAC opinion is expected to be finalized in March 2018. The OEL setting process will continue with inclusion of the OELs for nickel compounds under the Carcinogen, Mutagen Directive and the nickel metal OEL under the Chemicals Agents Directive.

Oral reference value for nickel

In 2017, NiPERA staff co-authored a peer reviewed manuscript with researchers from the University of Cincinnati on the subject of oral reference values for nickel (Haber et al., 2017). Reference values for adults, children, and nickel sensitive sub-populations were derived. The values are higher than those proposed by the European Food Safety Authority (EFSA) in 2015, even though they were based on the same data. The differences were due to different modelling approaches. The Haber et al. values were subject to additional peer review for entry into ITER (International Toxicity Estimates for Risk); ITER values undergo additional review by risk assessment experts for quality and merit and are often used by regulatory agencies in risk assessments. This new information has been shared with EFSA for their consideration. Oral reference values are important for setting standards for drinking water standards and food contact materials.

Acceptance of bioelution

NiPERA was actively involved in the EU discussions regarding the regulatory acceptability of bioelution-based approaches for the refinement of alloys classification to consider the release of rather than content of the constituents. This is important in view of the proposed EU cobalt metal classification and its specific concentration limit of 0.01%. Many alloys and nickel metal have cobalt present at levels above this cut-off. NiPERA participated in the ECHA Bioelution Expert Group, working side-by-side with Member State experts. After the consolidated document was delivered to CARACAL (EU Competent Authorities for REACH and Classification, Labelling and Packaging) in June, the European Centre for the Validation of Alternative Methods (ECVAM) agreed to work with Eurometaux and NiPERA on the validation of a gastric fluid protocol. A gastric fluid protocol would be submitted to ECVAM in February 2018.

REACH and Korea REACH

The REACH Science team updated and finalized REACH 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 are able to continue their market access in the EU. The Nickel Consortia approach is best practice by industry standards and well regarded by ECHA.

The REACH Science team also collected all NiPERA-owned final reports and their summaries, together with summaries from published manuscripts which were used in the registration of the 13 nickel substances subject to the EU REACH program. The purpose of this collection is to facilitate data sharing between the EU nickel industry and companies from global jurisdictions that establish new Chemical Management Legislation such as Korea REACH. Essentially, all the data that can be shared for each of the 13 nickel substances are now available, once data sharing arrangements including cost structures are finalized.

Metals mixtures modelling

The NiPERA-sponsored Metals Mixtures Modeling Evaluation (MMME) project contributed an 11-paper special series that was published in the peer-reviewed journal Environmental Toxicology and Chemistry (ET&C) in 2015. Results from ET&C's 2017 annual citation analysis showed that one paper in the series (Farley et al. 2015) was the top cited paper of 2016, and that five of the papers were in the top 10 most cited papers since 2015. An additional high-level synthesis paper of metal mixture risk assessment was published in ET&C's Focus Paper series in November of 2017, with support from NiPERA. The frequency of citation is a key metric of scientific excellence.

Nanoparticulates

In 2017 NiPERA initiated several projects for the nickel nanoparticulate research program. Projects included phys-chem analyses, bioelution analyses, and updated critical reviews of human health toxicity and environmental toxicity literature. This program proactively addresses current toxicological data gaps and risk characterization to anticipate potential differences in regulations applied to nano- versus micron-size materials containing nickel.

Nickel allergic contact dermatitis

As stakeholders, NiPERA and NI engaged in a variety of activities related to ECHA's draft "guideline on articles intended to come into direct and prolonged contact with the skin in relation to restriction of nickel and its compounds (entry 27 of Annex XVII)." The NiPERA contributions included:

- Presenting a webinar for interested stakeholders on nickel allergy, the draft list of articles and associated concerns, and the latest results from NiPERA dermatitis research being conducted to better understand nickel allergy and its sources.
- Submitting scientific comments and meeting with regulators to share scientific perspectives
- Presenting NiPERA research results at a NI Dermatitis Workshop with participation by ECHA representatives and leading researchers in this field
- Conducting research on the definition of "prolonged contact." The new data, already submitted for publication, inform the regulatory definition of "prolonged contact" and its consideration in ECHA's listing of articles of concern. The research demonstrates that ECHA's definition of "prolonged contact" is overly precautionary because the short time frames noted in the definition did not cause an allergic reaction in any individuals tested, and is therefore not scientifically justified
- Initiating research to better understand if a failure to comply with the European nickel restriction could be a source of the ongoing prevalence of nickel allergy, rather than a problem with the regulation itself
- Organizing research to investigate nickel dermatitis in children and teens to ensure that the articles and types of uses found to be significant sources of nickel allergy are recognized and addressed appropriately. The draft guideline list of articles was revised in October 2017 to exclude shower-head handles, gear sticks for car, and keys. ECHA distributed a "state of play" document on the draft guideline list of articles for the March 2018 CARACAL meeting that noted areas where input was being requested on whether to include "buckles for handbags"; "keychains, key rings, key fobs"; "outer case of electric/manual razor"; and "keys of PCs and laptops". Written comments were submitted on this new document by NiPERA by the end of March deadline. A revised draft of the ECHA guideline list is expected to be presented by ECHA, for discussion and possible approval, at the next CARACAL meeting in June 2018.

Environmental Quality Standards & bioavailability

NiPERA has led a series of initiatives around the world to ensure that Environmental Quality Standards (EQS) for nickel reflect the latest scientific information, and that they are not overly precautionary.

- In 2017 NiPERA became aware of a proposed revision of the Nickel EQS written by the Joint Research Centre (JRC) of the European Commission. The draft revision addresses the Ni EQS

that was established in 2013 under the Water Framework Directive, and for which European Member States are currently implementing compliance strategies. NiPERA established direct contact with the JRC to raise their awareness about new nickel data and information.

- NiPERA led the Eurometaux delegation participating in development of guidance for implementing bioavailability-based EQS for metals (including nickel) in Europe under the Water Framework Directive. This includes re-addressing disagreements over the use of competing user-friendly bioavailability tools.
- At the end of the year, NiPERA organized and chaired a Society for Environmental Toxicology and Chemistry (SETAC) workshop titled “Bioavailability-based Aquatic Toxicity Models for Metals.” The outcome of this workshop provides the technical support that US Environmental Protection Agency (US EPA) and other global regulatory authorities can consider in developing and applying bioavailability-based standards for metals.
- In the US, NiPERA also coordinated the multi-metallic initiative to develop a Cooperative Research and Development Agreement (CRADA) between metals research organizations and US EPA. This agreement establishes the administrative platform for the development of bioavailability-based Water Quality Criteria (WQC) for nickel, and other metals. The CRADA was signed by US EPA and NiPERA in December and will provide a platform for NiPERA science to be considered when developing bioavailability-based WQC for nickel.
- In Australia, NiPERA gained support from the Australian Committee for Water Quality Guidelines to propose an approach for setting a bioavailability-based Water Quality Guideline in Australia and New Zealand.

Rapid removal of metals from the water column

NiPERA organized an information exchange with the ECHA and EU Member States on the Rapid Degradation criteria of the chronic aquatic Environmental Hazard Classification category of the Global Harmonised System and EU Environmental Classification Labelling and Packaging schemes. Chemicals that cannot demonstrate Rapid Degradation receive a more stringent chronic environmental classification. As metals and inorganics do not degrade, rapid removal of metals from the water column has been proposed as a surrogate process. The concept of Rapid Removal has been demonstrated by the development of a laboratory-based test and a weight of evidence approach for assessing the removal of metals. This approach demonstrates that metals are removed from the water column via natural processes involving intrinsic characteristics of metals, and effectively reduces concentrations below hazardous thresholds. The meeting was held in the margins of SETAC Europe (Brussels, May) and was attended by NiPERA, six other metals’ commodity associations, ECHA, EU Member State representatives, and Eurometaux and highlighted the research and data analyses conducted in support of the Rapid Removal testing program from 2011-present. A further meeting in August between NiPERA, Eurometaux, and ECHA lead to agreement on a schedule for discussion and review of results from the industry sponsored rapid removal program. Based on these discussions, and at the request of ECHA, NiPERA and the European Copper Institute have spearheaded an effort to assemble a data package on test method development and research and modelling results that is to be shared with ECHA in 2018. This will lead to formal discussions recognizing the critical importance of this process to the proper environmental hazard assessment of metals.

Tropical risk assessment

NiPERA-sponsored research yielded important and novel findings, including data demonstrating that species critical to tropical ecosystems, like corals, are not uniquely sensitive to nickel exposure. Efforts are well underway to complete the first phase of the tropical environmental research program in 2018, and to communicate its findings to key stakeholders. NiPERA has also developed relationships with CNRT, an independent research organization in New Caledonia, to broaden the scope of the nickel environmental risk assessment tools developed by the NiPERA-funded research.

2017 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. While a typical year may see six or seven such publications, in 2017 a total of 13 manuscripts were published. 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.

1. Oller AR. 2017. Letter to Editor of Basic & Clinical Pharmacology & Toxicology journal, regarding the mini review titled Is nickel chloride really a non genotoxic carcinogen? By Stannard et al. (DOI: 10.1111/bcpt.12689). Basic & Clinical Pharmacology & Toxicology, DOI: 10.1111/bcpt.12760
2. Haber LT, Bates HK, Allen BC, Vincent MJ, Oller AR. 2017. Derivation of an oral toxicity reference value for nickel. Regul Toxicol Pharmacol. Jun 15. 87 Suppl 1: S1-S18. doi: 10.1016/j.yrtph.2017.03.011. Epub 2017 Mar 12.
3. Gissi F, Stauber J, Reichelt-brushett A, Harrison PL, Jolley DF. 2017. Inhibition in fertilisation of coral gametes following exposure to nickel and copper. Ecotoxicology and Environmental Safety 145: 32-41. doi:10.1016/j.ecoenv.2017.07.009.
4. Schlekot CE, Merrington G, Leverett D, Peters A. 2017. Chemical standard derivation for the protection of aquatic life: A guided world tour. Integrated Environmental Assessment and Management. DOI: 10.1002/ieam.1919
5. Efremenko A, Campbell Jr JL, Dodd DE, Oller AR, Clewell HK. 2017. Time- and concentration-dependent genomic responses of the rat airway to inhaled nickel sulfate. Environ Mol Mutagen. DOI 10.1002/em.22139.
6. Hale B, Gopalapillai Y, Pellegrino A, Jennett T, Kikkert J, Lau W, Schlekot C, McLaughlin M. 2017. Validation of Site-Specific Soil Ni Toxicity Thresholds with Independent Ecotoxicity and Biogeochemistry Data for Elevated Soil Ni. Environmental Pollution. 231: 165-172.
7. Binet M, Adams M, Gissi F, Golding L, Schlekot C, Garman E, Merrington G, Stauber J. 2017. Toxicity of nickel to tropical freshwater and sediment biota – a critical literature review and gap analysis. Environmental Toxicology and Chemistry. 10.1002/etc.3988.
8. Mendonca R, Daley J, Hudson M, Schlekot C, Burton, Jr. GA, Costello D. 2017. Metal Oxides in Surface Sediment Control Nickel Bioavailability to Benthic Macroinvertebrates Environ Sci Technol 51 (22), pp 13407–13416.
9. Brix KV, Tellis MS, Crémazy A, Wood CM. 2017. Characterization of the effects of binary metal mixtures on short-term uptake of Cd, Pb, and Zn by rainbow trout (*Oncorhynchus mykiss*). Aquat Toxicol. 193: 217-227. doi: 10.1016/j.aquatox.2017.10.015. Epub 2017 Oct 27.
10. Warshaw EM, Aschenbeck KA, DeKoven JG, Maibach HI, Taylor JS, Sasseville D, Belsito DV, Fowler JF Jr, Zug KA, Zirwas MJ, Fransway AF, DeLeo VA, Marks JG Jr, Pratt MD, Mathias T. 2017. Piercing and Metal Sensitivity: Extended Analysis of the North American Contact Dermatitis Group Data, 2007-2014. Dermatitis. Nov/Dec. 28(6): 333-341.
11. Verougstraete V, Henderson R, Mackie C, Newson T, Oller A. 2017. Human health (toxicity) assessment of complex inorganic materials. Book Chapter. Risk Management of Complex Inorganic Materials. A practical guide. Edited by V. Verougstraete. Elsevier Inc.

12. Verougstraete V, Danzeisen R, Bruzlauff A, Oller A, Heim K, Vetter D, Müller C, Battersby RV, Oorts K, Lison D. 2017. Mechanisms underlying toxicity of complex inorganic materials. Book Chapter. Risk Management of Complex Inorganic Materials. A practical guide. Edited by V. Verougstraete. Elsevier Inc.
13. Peters A, Merrington G, Schlekot C, De Schampheleere K, Stauber J, Batley G, Harford A, van Dam R, Pease C, Mooney T, Warne M, Hickey C, Glazebrook P, Chapman J, Smith R, and Krasso R. 2017. Validation of the nickel biotic ligand model for locally relevant species in Australian freshwaters. Environmental Toxicology and Chemistry. In Press.

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 significantly after the liability for a project is recorded to the budget and often significantly after the deliverables for a project are received by NiPERA staff.

Table 1: NiPERA's 2017 Operating Expenses

	Total
Revenue	
NI Dues	\$3,510,256
Cost Recovery Revenue	270,107
Interest Income	
Total Revenue	3,780,362
Operating Expenses	
Labor & Fringe	378,965
Administrative Expenses	75,426
Travel	31,321
Other Expenses	
Research - Nickel Metal	346,519
Research - Nickel Chemicals	
Research - Nickel Alloys	9,472
Research - Nanoparticles	211,515
Research - NACD	100,640
Research - Occupational Exposure Limits	66,643
Research - Incremental Reach Costs	
Research - Environmental Quality Studies	356,564
Research - Emerging Issues	(7,031)
Research - Contingencies	
Project Travel	148,788
Project Salary & Benefit	1,082,085
Project Office Costs	109,033
REACH	494,013
Transfer Costs	549,220
Loss on Disposal of Fixed Asset	
Realized Loss / (Gain) on Foreign Exchange	2,802
Depreciation Expense	71,889
Total Operating Expenses	4,027,864