NICKEL HEALTH AND ENVIRONMENTAL SCIENCES

2019 ANNUAL REPORT

COVERING ACTIVITIES FROM

JANUARY 1, 2019 – DECEMBER 31, 2019

AND BUDGETARY INFORMATION FOR FISCAL YEAR 2019

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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 2019, 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 2019 Business Plan was delivered, within budget.

> *In 2019 we witnessed the impact of years of scientific research by NiPERA on several key areas such as the completion of the environmental risk assessment program for the tropical region and the submission by EURL ECVAM of the gastric bioelution protocol to OECD that can eventually help refine the classification of alloys. NiPERA continues to scientifically contribute to regulatory and research activities around the world.*
>
> Dr. Adriana Oller
> Executive Director, NiPERA Inc.

Science Highlights

Final European Union (EU) Environmental Quality Standards (EQS) Implementation Guidance

The finalization of official guidance organized by the European Commission on implementation of bioavailability-based EQS under the Water Framework Directive further cements the use of the bioavailability-based standard for nickel in Europe. The easier it is for Member States to implement the nickel EQS, the less likely they are to deviate from this approach. Workshops with the Member State personnel who are directly involved in the implementation process have been well received and will be continued in 2020.

Global Bioavailability-Based Protective Values

Efforts to promote the use of bioavailability-based standards continued in other regions. A comparison of bioavailability modeling approaches that will be released by US Environmental Protection Agency (US EPA) in 2020 will include a case study on nickel. The methods used for this comparison will be based on the outcome of a 2017 Society of Environmental Toxicology and Chemistry (SETAC) Workshop that NiPERA co-chaired along with US EPA and other metals associations, the recommendations from which were published in a peer-reviewed journal in 2019. Work in Australia/New Zealand has culminated in the development of the first bioavailability-based Water Quality Guideline for this region that may become official in 2020. NiPERA continues work to validate existing nickel bioavailability models with Chinese toxicity test species using waters that reflect the range of surface water chemistry parameters in China. In Japan, research completed in 2019 demonstrated that an earlier proposal for an EQS was far too stringent. In 2020, NiPERA will hold a workshop with the Japanese Ministry of the Environment to communicate the outcome of this research and facilitate work towards a more relevant EQS.

Tropical Environmental Risk Assessment Research Program (2014-2019)

The objective of this program was to facilitate the migration of refined risk assessment approaches used globally to the South East Asia and Melanasia (SEAM) region. Applying these refined risk assessment approaches required validation of existing data and bioavailability models to the unique ecosystems and chemistries found in this region. This program was identified as a high priority because nickel laterite ore deposits are becoming increasingly important sources of nickel for the global marketplace and this may increase metal exposures in these regions. The program focused on the development of a conceptual model to identify important habitats and receptors, exposure assessment, effects assessment, and risk characterization. The outcome of the toxicity testing indicates that corals and other tropical species are not different in terms of their sensitivity from temperate organisms. This provides the basis for pooling ecotoxicity datasets, which has the advantage of increased numbers of organisms and taxonomic groups. The results from this program were communicated at a workshop for regional government, academic, and consulting scientists and will result in a 2020 publication series.

The outcome of the Tropical Environmental Risk Assessment Research Program will also be used as the basis for establishing a nickel EQS for New Caledonia. NiPERA is performing toxicity tests with native New Caledonian species in relevant natural waters and will also work with regional experts to identify other relevant ecotoxicity data. The work began in 2019, with a target completion date of 2021.

Nickel Metal Classification

In 2019 we progressed in our plans to address two main challenges affecting nickel metal classifications. They included: i) the lack of robust data on reproductive toxicity, and ii) changes to cancer classification of cobalt metal as Carco 1B, for all routes, which can affect the classification of nickel and its alloys.

The acceptance by European Chemicals Agency (ECHA) of the testing proposal for a reproductive study with nickel metal allows for the collection of robust data on which to base the assessment of reproductive toxicity of nickel metal. This data collection, in turn, will prevent a precautionary classification based on substandard data. ECHA's draft decision was encouraging. NiPERA commented on details of the study design and clarified the responsibilities of registrants and the timeline for the study. Bioelution and toxicokinetic studies with nickel metal samples have been completed with final data analyses expected in 1Q 2020. Preliminary results show that the release of nickel ions from nickel metal massive is lower than from micron and nano forms consistent with a lower bioavailability in the toxicokinetic studies. The data from these preliminary studies will inform dose selection in the reproductive study expected to begin in 2020.

Regarding the classification of cobalt metal as Carco 1B in the EU CLP (Classification, Labelling and Packaging) regulation, in 2019 agreement was reached between NiPERA and Cobalt Institute to co-sponsor an oral carcinogenicity study with cobalt chloride. This will clarify the need to include the oral route of exposure in the cancer classification of cobalt metal. A classification of cobalt for carcinogenicity by "all routes" can have significant consequences for nickel and stainless steel in applications with long history of safe use (e.g., eating utensils), as cobalt is found as an impurity in these materials. The plan is to submit a testing proposal for this study to ECHA.

Furthermore, work continued on the publication of results from bioelution testing of soils and alloys (see text below); bioelution can provide a pragmatic and scientifically based approach to refine the current system for alloy classification based on content. This may be a viable option to prevent

unwarranted Carcinogen, Mutagen, Reproductive Toxicant (CMR) classification of many alloys with very low metal releases, and associated low toxicity.

In 2019 NiPERA filled a data gap for nickel metal with the publication of a manuscript describing the results from mutagenicity studies of nickel metal. In addition, NiPERA's commissioning of a comprehensive review paper will update the available cancer data for nickel metal. Some additional in vitro studies are expected to be undertaken in early 2020.

Alloy Classification

The submission by EURL ECVAM (European Centre for the Validation of Alternative Methods) of the bioelution gastric protocol to the Organization for Economic Co-operation and Development (OECD) and the acceptance of the gastric protocol by ECVAM's experts expected in 1Q 2020 are very important steps towards the refinement of the classification of alloys based on metal release rather than metal content. Some EU regulatory authorities have been hesitant to accept bioelution data-based assessments due to the lack of a validated and internationally recognized test protocol. Under the leadership of Eurometaux and NiPERA, a bioelution protocol for a gastric test submitted to ECVAM for validation has been approved and submitted to OECD for the development of an OECD test guideline. Two main applications of the protocol were included: for grouping and read across of metal-containing substances and for the calculation of the Relative Bioaccessible Concentration of metals in alloys. The latter provides the information required for the refinement of alloy classification, as a scientific method of measuring the relative amount of metal release available for potential toxicity. This is of utmost importance in view of the impact that the proposed cobalt metal classifications can have on alloys. These efforts were complemented by the publication of a manuscript on cobalt and nickel releases from various alloys, calculation of Relative Bioaccessible Concentrations, and demonstration of refinement of alloy classification.

Nickel Nanoparticulate Research Program Progresses

This program proactively addresses current toxicological data gaps and risk characterization issues specific to nanoforms of nickel metal and compounds. The acute inhalation of nickel oxide nanoparticles was investigated in 2019. Although rodent mortality was observed following acute inhalation of nano nickel oxide, the overall results suggest fairly similar toxicity profiles with regard to classification for micron and nano forms of nickel oxide. Comprehensive reviews on the human health and environmental effects of nickel nanoparticles were also initiated. In terms of environmental effects, for most organisms tested, nickel nanoparticles are not more toxic than dissolved nickel and there is little evidence that the currently produced nickel nanoparticles lead to environmental exposure. The two reviews did reveal data gaps and study limitations that could be considered for future projects. Proactively understanding the toxicity of nanoforms of nickel can ensure that risks of nanoparticle exposure to humans and the environment are well understood.

Developments on Nickel Allergic Contact Dermatitis

While the prevalence of nickel allergy in EU is lower than before the nickel restriction came into effect, young people are still becoming nickel allergic. Of concern to the marketing and perception of nickel-containing stainless steels is the suggestion that the reason for the continued prevalence of nickel allergy is because the EU nickel restriction is not sufficiently stringent. NiPERA undertook a study to determine the level of compliance with the EU nickel restriction. A variety of items listed as examples

under the EU nickel restriction were purchased in three countries expected to have high compliance rates. Items were bought from different types of stores and markets, and the nickel release was measured to assess compliance. A similar rate of non-compliance (~15%) was observed for all items in all three countries. Of all the types of articles tested, the highest rates of non-compliance were for earrings, clothing (jeans fasteners), and watches. Results of this study support previous findings that a significant number of items covered by the EU nickel restriction are not compliant and could at least partially explain the continued prevalence (albeit at lower levels) of nickel allergy in the young population. The results from the study will be communicated to stakeholders in 2020.

New Test Methodology for Environmental Hazard Classification of Nickel

NiPERA coordinated a multi-metallic initiative to develop a new test methodology and 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. NiPERA, along with other metals associations, developed a testing approach and supporting evidence that metals are rapidly removed from the water column, resulting in dissolved concentrations that are below hazard cut offs. Our position is that these results should be taken into account for classification. Work will continue in 2020 to ensure consistent application and documentation of the Rapid Removal concept for self-classification under GHS and CLP for all of the metals.

Read Across of Ecotoxicity Data Among Nickel Compounds

At a Metals and Inorganics Sectorial Approach (MISA) workshop held in 2019, ECHA indicated that "registrants should better motivate that the counter-ion used as source substance in ecotoxicity tests would have no effect on the toxic response." Under the current REACH dossiers, environmental toxicity studies treat all soluble nickel substances, regardless of the counter-ion, as a single "group." If this read-across assessment is not considered by ECHA to be adequately justified, it could lead to the need for generation of ecotoxicity data for each endpoint using the remaining soluble nickel substances. Insufficient justification could affect multiple lines of ecological risk assessment practices as well as numerous assumptions behind bioavailability modeling and toxicity prediction. Thus, NiPERA is participating in an initiative to provide a compelling justification for reading across counter ions. The goal is to generate a multi-metallic publication (with ECHA's input) that will systematically cover broad chemical and toxicological properties of metals and counter ions.

EU REACH

The Nickel REACH Consortia received ECHA's draft decision on the EOGRTS (Extended One Generation Reprotoxicity Toxicity Study) testing proposal for nickel, which was accepted with some modifications. This acceptance is in line with our scientific assessment that additional data is needed to clarify the reproductive toxicity properties of nickel metal. Furthermore, the Nickel REACH Consortia continued collaborating with ECHA on MISA. This cooperative program aims to resolve outstanding technical and methodological issues of relevance for metals and inorganics as well as improving compliance and quality of the dossiers. It also provides a good forum to engage with ECHA on open scientific and regulatory questions. The Nickel REACH Consortia have been diligently and continuously improving and updating the registration dossiers on a yearly basis since 2010, and the MISA priorities are already integrated in our workplan. We remain committed to deliver good quality and updated registration

dossiers for nickel and nickel substances which is important as this forms the basis for many regulations and legislations in the EU and abroad, especially Asia, as the EU is promoting REACH very actively in different countries.

Korea REACH

Registration of nickel substances has in Korea in their version of REACH is ongoing, with many substances submitted in the last two years, and other nickel substances being registered soon. The Nickel Institute has been working to ensure that our scientific data are used and correctly interpreted and that classification proposals consider the latest scientific developments, consistent with how the data has been used appropriately in other regulations.

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. The publications listed below 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.

2019. Burton GA Jr, Hudson ML, Huntsman P, Carbonaro RF, Rader KJ, Waeterschoot H, Baken S, Garman E. Weight-of-Evidence Approach for Assessing Removal of Metals from the Water Column for Chronic Environmental Hazard Classification. Environ Toxicol Chem 38: 1839-1849. doi: 10.1002/etc.4470.

2019. Buxton S, Garman E, Heim KE, Lyons-Darden T, Schlekat CE, Taylor MD, Oller AR. Concise review of nickel human health toxicology and ecotoxicology. Inorganics 7(7): 89.

2019. Crémazy A, Brix KV, Wood CM. Using the Biotic Ligand Model framework to investigate binary metal interactions on the uptake of Ag, Cd, Cu, Ni, Pb and Zn in the freshwater snail Lymnaea stagnalis. Science of The Total Environment 647: 1611–1625. doi: 10.1016/j.scitotenv.2018.07.455.

2019. Gissi F, Reichelt-Brushett AJ, Chariton AA, Stauber JL, Greenfield P, Humphrey C, Salmon M, Stephenson SA, Cresswell T, Jolley DF. The effect of dissolved nickel and copper on the adult coral Acropora muricata and its microbiome. Environmental Pollution 250: 792-806.

2019. Huntsman P, Beaudoin R, Rader KJ, Carbonaro RF, Allen Burton G Jr, Hudson M, Baken S, Garman E, Waeterschoot H. Method Development for Determining the Removal of Metals from the Water Column under Transformation/Dissolution Conditions for Chronic Hazard Classification. Environ Toxicol Chem 38: 2032-2042. doi:10.1002/etc.4471.

2019. Martin OV, Adams J, Beasley A, Belanger S, Breton R, Brock T, Buonsante VA, Burgos MK, Green J, Guiney P, Hall T, Hanson ML, Harris MJ, Henry TA, Huggett D, Junghans M, Laskowski R, Maack G, Moermond C, Panter G, Pease A, Poulsen V, Roberts M, Rudén C, Schlekat C, Schoeters I, Solomon K, Staveley J, Stubblefield W, Sumpter J, Warne MSJ, Wentsel R, Wheeler J, Wolff BA, Yamazaki K, Zahner H. Improving environmental risk assessments of chemicals: steps towards evidence-based ecotoxicology. Environment International 128: 210-217.

2019. Nys C, Van Regenmortel T, De Schamphelaere K. The Effects of Nickel on the Structure and Functioning of a Freshwater Plankton Community Under High Dissolved Organic Carbon Conditions: A Microcosm Experiment. Environ Toxicol Chem 38: 1923-1939. doi: 10.1002/etc.4504.

2019. Peters A, Merrington G, Leverett D, Wilson I, Schlekat C, Garman E. Comparison of the chronic toxicity of nickel to temperate and tropical freshwater species. Environ Toxicol Chem 38: 1211-1220. doi: 10.1002/etc.4384.

2019. Warshaw EM, Zhang AJ, DeKoven JG, Maibach HI, Belsito DV, Sasseville D, Fowler JF Jr, Fransway AF, Mathias T, Pratt MD, Marks JG Jr, Zug KA, Zirwas MJ, Taylor JS, DeLeo VA. Epidemiology of nickel sensitivity: Retrospective cross-sectional analysis of North American Contact Dermatitis Group data 1994-2014. J Am Acad Dermatol 80(3): 701-713.

The following seven publications bear a 2020 date, however they were published online in December 2019:

2020. Adams W, Blust R, Dwyer R, Mount D, Nordheim E, Rodriguez PH, Spry D. Bioavailability Assessment of Metals in Freshwater Environments: A Historical Review. Environ Toxicol Chem 39: 48-59. doi: 10.1002/etc.4558.

2020. Brix KV, DeForest DK, Tear L, Peijnenburg W, Peters A, Middleton ET, Erickson R. Development of Empirical Bioavailability Models for Metals. Environ Toxicol Chem 39: 85-100. doi: 10.1002/etc.4570.

2020. Garman ER, Meyer JS, Bergeron CM, Blewett TA, Clements WH, Elias MC, Farley KJ, Gissi F, Ryan AC. Validation of Bioavailability-Based Toxicity Models for Metals. Environ Toxicol Chem 39: 101-117. doi: 10.1002/etc.4563.

2020. Heim KE, Danzeisen R, Verougstraete V, Gaidou F, Brouwers T, Oller AR. Bioaccessibility of nickel and cobalt in synthetic gastric and lung fluids and its potential use in alloy classification. Regul Toxicol Pharmacol 110: 104549.

2020. Mebane CA, Chowdhury MJ, De Schamphelaere KA, Lofts S, Paquin PR, Santore RC, Wood CM. Metal Bioavailability Models: Current Status, Lessons Learned, Considerations for Regulatory Use, and the Path Forward. Environ Toxicol Chem 39: 60-84. doi: 10.1002/etc.4560.

2020. Schlekat C, Stubblefield W, Gallagher K. State of the Science on Metal Bioavailability Modeling: Introduction to the Outcome of a Society of Environmental Toxicology and Chemistry Technical Workshop. Environ Toxicol Chem 39: 42-47. doi: 10.1002/etc.4561.

2020. Van Genderen E, Stauber JL, Delos C, Eignor D, Gensemer RW, McGeer J, Merrington G, Whitehouse P. Best Practices for Derivation and Application of Thresholds for Metals Using Bioavailability-Based Approaches. Environ Toxicol Chem 39: 118-130. doi: 10.1002/etc.4559.

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.

Description	Total USD
Revenue	
Nickel Institute Dues	$4,176,826
Total Revenue	*4,176,826*
Operating Expenses	
Labor & Fringe	249,439
Administrative Expenses	78,203
Travel	31,667
Research - Nickel Metal	100,513
Research - Nickel Chemicals	6,643
Research - Nickel Alloys	92,305
Research - Occupational Exposure Limits	(2,977)
Research - Environmental Quality Studies	350,179
Research - Emerging Issues	120,230
Research - Nanoparticulates	27,360
Research - Nickel Allergy Contact Dermatitis	21,161
Research - Program Support	61,454
Project Travel	103,312
Project Salary & Benefit	1,109,938
Project Office Costs	96,497
Transfer Costs	1,131,088
Realized Loss/(Gain) on Foreign Exchange	5,989
Depreciation Expense	64,776
Total Operating Expenses	*3,647,777*
Operating Income	**$529,049**

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