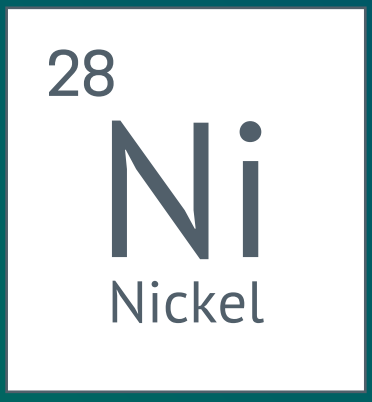
2022 ANNUAL REPORT

Covering activities from January 1, 2022 – December 31, 2022 and Budgetary Information for Fiscal Year 2022



May 2023

NiPERA
NICKEL HEALTH AND ENVIRONMENTAL SCIENCES

NiPERA Inc. is the Nickel Institute's independently-incorporated science division. NiPERA is committed to supporting scientifically-sound research and promoting general awareness of the care required in safely producing, using, and disposing of nickel.

We at NiPERA take the human health and environmental science of nickel very seriously.

In 2022 we collectively advanced the understanding of nickel's health and ecosystem effects, and this will allow nickel producers and the value chains they serve to continue to use this critical element safely and confidently.

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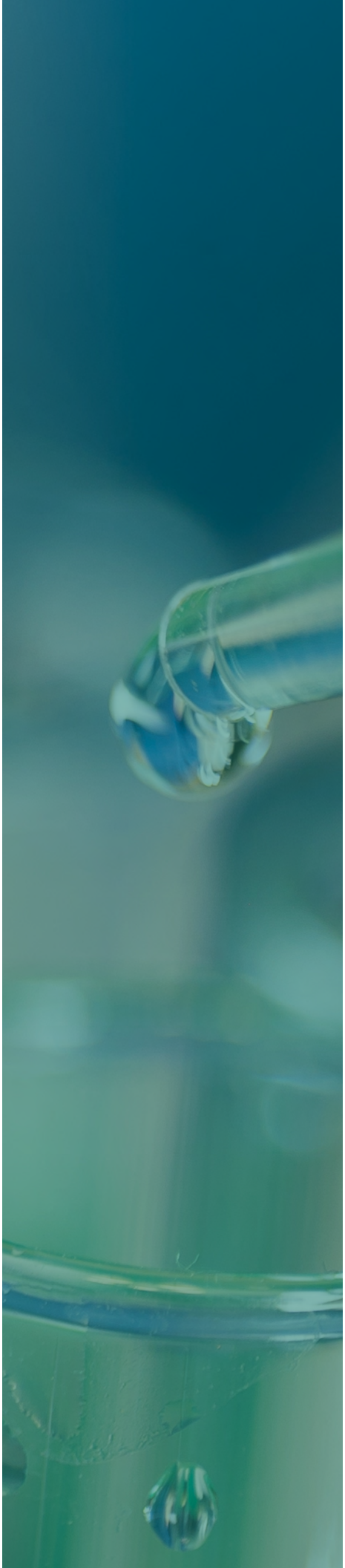

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SCIENCE HIGHLIGHTS

Nickel Metal Classification

To prevent inappropriate classification of nickel metal as a reproductive toxicant, a guideline compliant Extended One Generation Reproductive Toxicity Study (EOGRTS) for nickel metal powder was initiated in 2021 and was successfully completed in Q2 of 2022. No toxicologically significant effects of treatment were observed over the course of the study, indicating that nickel metal should not be classified as a reproductive toxicant. The next steps will be to communicate the outcome of the study to the European Chemicals Agency (ECHA) prior to August 2023, which is the legally binding deadline set by ECHA.

Cobalt Carcinogenicity Classification

In 2021, cobalt metal was classified as a carcinogen (Carc 1B) by all routes of exposure and there was no evidence available to exclude the oral route and limit the classification to the inhalation route. Additionally, decisions made within EU Commission working groups set the stage for the Generic Concentration Limit of 0.1% to be reduced to a Specific Concentration Limit of 0.01%, which would threaten to capture both nickel metal and stainless steel due to the occurrence of cobalt (as impurity) in these substances. To mitigate these impacts, the Cobalt Institute and NiPERA submitted a testing proposal for an oral carcinogenicity study with cobalt chloride in 2020, which the European Chemicals Agency (ECHA) tentatively approved via a draft decision in Q4 of 2022. ECHA has a number of steps to take before rendering a final decision, which we expect to see within 2023. The main study, which will be co-managed by NiPERA toxicologists, is unlikely to begin before 2025.

Nickel Dermatitis Research

In 2022 a study was completed that provides information suggesting a much longer time is needed to elicit an allergic reaction in an already nickel-sensitized individual than the current ECHA guidance definition of prolonged contact. This definition is used in determining the types of articles should be included in the European Union nickel restriction, which restricts nickel release of these articles to those releasing <0.5 mg Ni/cm^2/week in synthetic sweat (EN 1811 protocol). Three phases of this clinical research study, each of which was conducted with different nickel substances, support the time being longer than that cited in the ECHA regulatory guidance definition. NiPERA plans to continue this work with a larger study that would include more subjects and a refined range of exposure times based on the first three phases.

Biological Effect Action Level Approach to Urinary Nickel Biomonitoring

NiPERA presented a detailed case study titled *Biological Effect Action Level (BEAL) Versus Biological Exposure Index (BEI)* at the Alliance for Risk Assessment: Beyond Science and Decision Workshop XIII on 16 February. The session included presentations by NiPERA toxicologists and the Nickel Institute industrial hygienist that covered the limitations of the exposure-based BEI approach to set urinary nickel levels (such as that used by the American Conference of Governmental Industrial Hygienists (ACGIH) to set nickel BEIs in 2021). NiPERA and the Nickel Institute explained the advantages of the health-based BEAL approach to set safe urinary levels for each worker, considering their individual characteristics and work shift pattern. The approach was discussed at length by a panel of risk assessment experts from government (e.g., US Environmental Protection Agency, US National Institute for Occupational Safety and Health), academia, and the private sector, who ultimately agreed that the BEAL approach was a valid alternative to BEIs. A detailed writeup of the case study will be hosted on the Alliance for Risk Assessment website to serve as a resource for regulators, scientists, and industrial hygiene professionals implementing urinary nickel biomonitoring standards in the future.

Nickel Ambient Air Standards

In early 2022, the Québec Ministry of the Environment and the Fight Against Climate Change (MELCC) proposed higher revised ambient air standards for nickel. NiPERA submitted comments in February that supported MELCC's proposed values by demonstrating that they are protective of public health, and even higher values could be warranted. The proposed values were formally adopted on 28 April. However, during the process of setting the standards, media reports on the new higher values lead some residents of the Limoilou District to be concerned about overall air quality in the region. Therefore, the Québec MELCC formed an independent task force to examine total air quality in the district and recommend steps to improve local air quality. NiPERA met with the task force reassuring them that the newly adopted ambient air standards for nickel in Québec are protective of public health with large margins of safety. NiPERA presented recent scientific information, engaged in discussion, and answered questions from the task force, as well as participated in discussions from those proposing that the standards should be lowered. The task force report was released in January 2023 and concluded that exposure to fine particulates

(i.e., $PM_{2.5}$) and nitrogen dioxide (NO_2) are the largest health concerns to the residents of Québec City and that the risks from nickel exposure are very low in comparison. They also found that ambient air nickel levels are below the new chronic air standard in the Limoilou neighborhood near the port. Nevertheless, because the report used very conservative assumptions regarding the mode of action of nickel toxicity and the fact that the short-term ambient air standard is occasionally exceeded, the report concluded that actions should be taken at the port to continue to reduce nickel emissions during operations. However, the highest priorities recommended by the report to maximize health gains are general reduction efforts for $PM_{2.5}$ and NO_2. Without NiPERA's participation in the process, the focus on nickel may have remained. The Minister of Environment will now review the report and meet with stakeholders to decide what recommended measures to implement. NiPERA will stand by to provide further information to the Minister on the health risks of nickel exposure and why the new air nickel standards are protective of public health with large margins of safety.

Bioavailability-based Environmental Quality Standards

In 2022, NiPERA published an analysis that assessed the extent of environmental risks from nickel in European freshwater, based on the latest information on nickel ecotoxicology, bioavailability, and supporting information. Nickel monitoring information from more than 19,000 sites across Europe were evaluated, and when bioavailability was accounted for, >99% of sites were shown to comply with the nickel Environmental Quality Standard. This suggests that nickel does not represent a continental scale risk to freshwater ecosystems within Europe, which suggests that the classification of nickel as a Priority Substance may not be necessary. Elsewhere in the world, NiPERA continued its work with the US Environmental Protection Agency through a Cooperative Research and Development Agreement to update the nickel Water Quality Criteria (WQC) and to incorporate bioavailability normalization into the nickel WQC. Additionally, progress has been made in China in NiPERA's collaborations with the Chinese Research Academy of Environmental Sciences (CRAES) in terms of establishing a bioavailability-based Environmental Quality Standard for nickel. Specifically, a paper summarizing Phase 1 of our work with CRAES was accepted for publication, and Phase 2 was initiated, with the aim of completing this research effort in 2023.

Impacts of Climate Change and Polar Risk Assessment Initiatives

In 2022, NiPERA took concrete steps to examine the impacts of climate change on the environmental risks presented by nickel. Climate change impacts metal ecotoxicity in many ways, and these impacts need to be reflected in nickel environmental risk assessments. NiPERA helped organize the 2022 meeting of the Ecotoxicity Technical Advisory Panel (ETAP) to focus on these needs and led the submission of a proposal to the International Council on Mining and Metals Materials Stewardship Foundation to provide leveraged funding to put the ETAP recommendations into practice. These initiatives complement NiPERA's Polar Environmental Research Project, which seeks to develop risk assessment approaches for nickel in polar regions where Nickel Institute member companies operate, and where impacts of climate change are pronounced. A research agenda was established in 2022 that will ensure that each component of the environmental risk assessment framework, including effects assessment, exposure assessment, and risk characterization are appropriate to account for the unique attributes of polar ecosystems.

Science Operations

The Science Support Program ensures that NiPERA's operational management of nickel human and environmental health science runs smoothly and without interruption.

NiPERA's life blood is the peer-reviewed scientific literature on the fate and effects of nickel. NiPERA contributes to this literature, and we depend on the ability to access papers published by other scientists. In 2022, NiPERA continued to utilize the RightFind™ platform, which is a one-source, web-based platform that integrates copyright licensing with the management of NiPERA's publications. Additionally, select Nickel Institute staff who require access to scientific literature are also included in the process.

EU REACH

Demonstrating safety for human health and the environment has always been a core endeavor for the Nickel REACH Consortia, where NiPERA plays a critical role in terms of managing the immense amount of scientific information available for the nickel substances registered via REACH. As such, we have been continuously improving and updating the registration dossiers on a yearly basis since 2010. The updates include new or revised compositions, classifications, toxicity data, and exposure assessments. We remain committed to delivering high quality and updated registration dossiers for nickel and nickel substances. This is important because this forms the basis for many regulations and legislation in the EU and abroad, especially Asia, as the EU is promoting REACH very actively in different countries. One specific example of innovation that NiPERA and its Nickel Institute colleagues have achieved is to incorporate the outcome of the Metals and Inorganics Sectoral Approach (MISA) Program, a cooperative initiative between ECHA, Eurometaux, and various industry associations. MISA strived to resolve technical and methodological issues of relevance for metals and inorganics as well as to improve the compliance and quality of the REACH registration dossiers. With the lessons learned from the MISA Program, NiPERA and its collaborators are well-prepared to address future issues that may arise. NiPERA and its collaborators are also committed to the Metals Environmental Exposure Data Program (MEED) which is a multi-metallic 3-year program. The goal of MEED is to show a good understanding of current and future trends in exposures, risks, and their control through the development of approaches and the collection of exposure data to help demonstrate that the production and use of metals brings no harm on health, on environment and biodiversity.

PEER-REVIEWED NiPERA MANUSCRIPTS

In 2022 NiPERA-sponsored research was well represented in the scientific literature.

A total of 14 peer-reviewed publications were published, and many of these include NiPERA staff as co-authors, which reflects their contributions as scientists.

Human Health

2022. **Buxton S**, **Verpaele S, Oller A.** Nickel and nickel compounds. In: Levy L, Greim H, eds. Patty's Industrial Hygiene and Toxicology, 7th Ed. Wiley. Book chapter (in press Oct).

2022. Kimber I, Basketter D. Allergic sensitization to nickel and implanted metal devices: A perspective. Dermatitis 33(6): 396-404.

2022. **Lyons-Darden T**, Blum JL, Schooley MW, Ellis M, Durando J, Merrill D, **Oller AR**. An assessment of the oral and inhalation acute toxicity of nickel oxide nanoparticles in rats. Nanomaterials (submitted for publication Dec).

2022. **Oller AR, Buxton S**, March TH, Benson JM. Comparative pulmonary and genotoxic responses to inhaled nickel subsulfide and nickel sulfate in F344 rats. Journal of Applied Toxicology (accepted Oct), doi: 10.1002/jat.4422.

2022. Taxel P, Huuskonen P. Toxicity assessment and health hazard classification of stainless steels. Regulatory and Pharmacology 133: 105227.

2022. Verougstraete V, Danzeisen R, Viegas V, Marsh P, **Oller A**. A tiered approach to investigate the inhalation toxicity of cobalt substances. Tier 1: Bioaccessibility testing. Regulatory Toxicology and Pharmacology 129: 105124.

Environmental Health

2022. Adams W, Baken S, Carey S, Boyle D, Chowdhury J, Cooper C, **Garman E**, Gopalapillai Y, Mackie C, McGeer, J, Mertens J, Merrington G, **Schlekat C**, Smith E, Stubblefield W, Verougstraete V, Waeterschoot H, Weidenauer M. Application of PBT for metal hazard assessment is questioned. Environ Toxicol Chem 41(11): 2629-2631.

2022. Brix KV, Blust R, Mertens J, Baken S, **Middleton ET**, Cooper C. Evaluation of effects-based methods as monitoring tools for assessing ecological impacts of metals in aquatic ecosystems. Integr Environ Assess Manag 19(1): 24-31.

2022. He J, Wang C, **Schlekat C,** Wu F, **Middleton E**, **Garman E**, Peters A. Validation of nickel bioavailability models for algae, invertebrates, and fish in Chinese surface waters. Environ Toxicol Chem (accepted for publication).

2022. Mano H, Shinohara N, Peters A, **Garman E**, **Middleton E**, **Schlekat C**, Naito W. Variation in chronic nickel toxicity to Daphnia magna among Japanese river waters and performance evaluation of bioavailability models in predicting the toxicity. Environ Sci Pollut Res Int 29(19): 27664-27676.

2022. Merrington G, Peters A, **Schlekat C**, **Middleton E**, **Garman E**. Assessing nickel risks in freshwater in order to deliver better environmental protection. Environ Toxicol Chem 41(4): 815-817.

2022. Peters A, Wilson I, Merrington G, **Schlekat C**, **Middleton E**, **Garman E**. Assessing the extent of environmental risks from nickel in European freshwaters: A critical reflection of the European Commission's current approach. Environ Toxicol Chem 41(7): 1604-1612.

2022. Peters A, Nys C, Leverett D, Wilson I, Van Sprang P, Merrington G, **Middleton E**, **Garman E**, **Schlekat C**. Updating the chronic freshwater ecotoxicity database and biotic ligand model for nickel for regulatory applications in Europe. Environ Toxicol Chem (accepted for publication).

2022. Stauber JL, Adams MS, Batley GE, Golding LA, Hargreaves I, Peeters L, Reichelt-Brushett AJ, Simpson SL. A generic environmental risk assessment framework for deep-sea tailings placement. Science of the Total Environment 845: 157311.

**NiPERA/Nickel Institute staff in bold*

ORGANIZATIONAL STRUCTURE

At the end of 2022, NiPERA said goodbye to Dr. Adriana Oller, who worked tirelessly for NiPERA for nearly 29 years. Adriana served as a senior human health toxicologist, NiPERA's Executive Director, and most recently as Toxicologist Emeritus. We are indebted to Adriana for her service and tutelage.

BUDGET

Description	Total US Dollars
Revenue	
Nickel Institute Dues	$4,177,285
REACH Project Fees	582,666
Cost Recovery Revenue	25,000
Interest Income	13
Total Revenue	$4,784,964

Operating Expenses	
Labor & Fringe	$380,830
Administrative Expenses	48,341
Travel	11,468
Research - Nickel Metal	486,155
Research - Nickel Chemicals	28,802
Research - Nickel Alloys	3,771
Research - Occupational Exposure Limits	60,000
Research - Environmental Quality Studies	371,379
Reserach - Nanoparticulates	19,990
Research - NACD	34,760
Reserach - Program Support	84,111
Project Travel	29,535
Project Salary & Benefit	1,374,080
Project Office Costs	78,349
REACH	624,539
Transfer Costs	1,006,997
Loss on Disposal of Fixed Asset	0
Depreciation Expense	28,441
Total Operating Expenses	$4,671,548

Operating Income	**$113,416**

The NiPERA budget reporting paradigms are based upon Generally Accepted Accounting Principles 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.

NiPERA

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