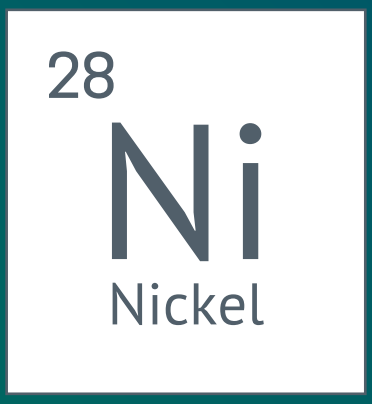
2023 ANNUAL REPORT

Covering activities from January 1, 2023 – December 31, 2023 and Budgetary Information for Fiscal Year 2023



April 2024

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.

2023 set a marker in terms of the scientific information society expects in terms of its acceptance of nickel as a material of choice. In addition to the standard human health and environmental data required to market nickel and nickel substances in increasing numbers of global markets, we now face increased inquiries about indirect factors such as climate change.

NiPERA's scientists are at once experts in traditional toxicological disciplines and are also well-equipped to navigate the new challenges Nickel Institute member companies must address to access existing and emerging markets.

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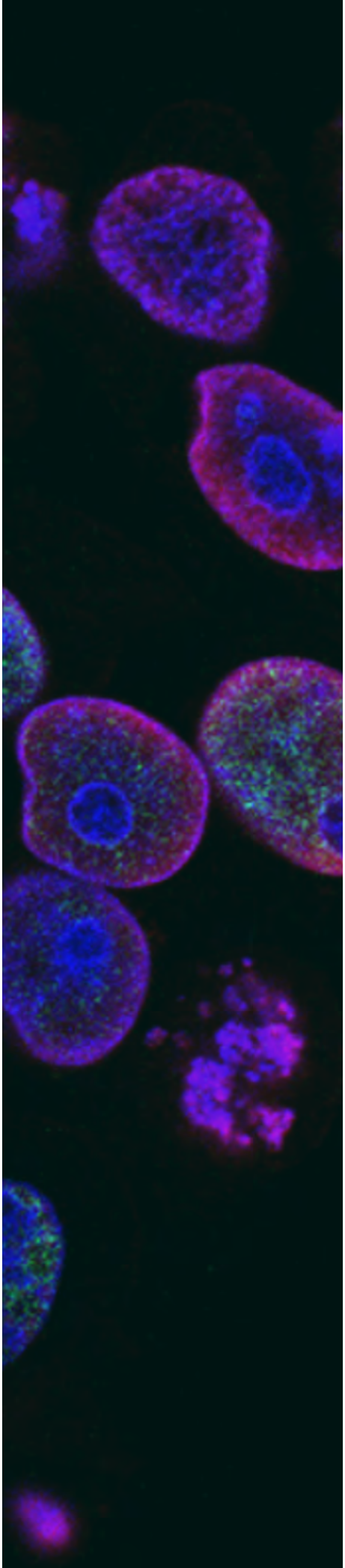

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SCIENCE HIGHLIGHTS

Nickel Metal Classification

One of the Nickel Institute's achievements over the past years is to ensure that nickel metal is not classified as a carcinogenic, mutagenic, reprotoxic (CMR) substance. In 2021, to support the appropriate classification of nickel metal, a guideline-compliant Extended One Generation Reproductive Toxicity Study (EOGRTS) for nickel metal powder was initiated. The study was successfully completed in Q2 of 2022. NiPERA received the final report from the testing laboratory in Q2 2023.

The outcome of the study was that no toxicologically significant effects of nickel metal treatment on reproduction or development (or any other endpoint) were observed. Hence, nickel metal should not be classified as a reproductive toxicant.

The study was submitted to the European Chemicals Agency (ECHA) by including the study report in the updated Nickel Metal REACH dossier in August 2023, which satisfies NiPERA's legal obligations. This study adds to the body of evidence against listing nickel metal as a CMR substance.

Cobalt Carcinogenicity Classification

In 2021, cobalt metal was classified as a carcinogen (Carc 1B) by all routes of exposure. No evidence was available to exclude the oral route and limit the classification to the inhalation route. Some nickel compounds, e.g., $NiSO_4$, are classified as carcinogens, but, due to negative oral carcinogenicity studies, these classifications are limited to the inhalation route. Additionally, decisions made within EU Commission working groups are expected in 2024 that will 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 an 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. In Q3 2023, the European Chemicals Agency (ECHA) approved the testing proposal and announced that the study's final report must be submitted by January 2028. The guideline-compliant test will begin in 2024.

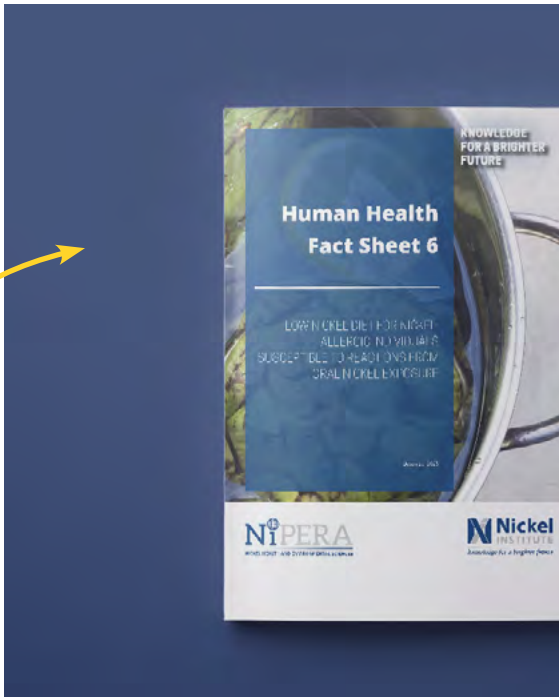
Nickel Dermatitis Research

NiPERA's work on defining the circumstances and scale of nickel release from consumer articles in direct and prolonged skin contact continued in 2023. Nickel release is required for nickel allergic contact dermatitis (NACD) to occur, and EU regulators use it as the basis for restricting items from the EU consumer market. An analysis of nickel release from consumer articles in the US demonstrated that the percentage of total tested high nickel-releasing items available on the market was generally similar to an earlier study on EU articles. The occurrence of high nickel-releasing items supports that enforcement of the EU nickel restriction and communication in the US is needed to decrease nickel dermatitis. This information will be analyzed together with the results of the plating and composition characterization of the same samples and will be published in a peer-reviewed journal.

NiPERA also published its sixth Human Health Fact Sheet, *Low Nickel Diet for Nickel-Allergic Individuals Susceptible to Reactions from Oral Nickel Exposure*. This fact sheet is an important resource for the subpopulation of nickel-allergic people who may have reactions from oral exposure to relatively high concentrations of nickel and have been advised by a medical professional to undergo a low nickel diet to reduce and prevent symptoms of systemic nickel allergic syndrome.

International Risk Assessment Guidance

NiPERA provided leadership and scientific input in developing an Association of Southeast Asian Nations (ASEAN) guidance on chemicals risk assessment. The ASEAN Regulatory Cooperation Project (ARCP) is a key initiative in Southeast Asia, promoting robust regulatory practices and setting a regional standard for sound chemical management. The guidance document on risk assessment provides knowledge and a template for developing risk assessment frameworks in Southeast Asia while influencing similar work in Latin America, which are both important nickel-producing regions. The document is based on existing risk assessment guidance, of which the Nickel Institute/NiPERA contributed information on metals-specific



considerations such as natural occurrence and essentiality, which otherwise would not have been integrated. NiPERA staff spearheaded the completion of the draft guidance, which was communicated to ASEAN industry and country representatives in a workshop held in Bangkok in November 2023.

In the US, NiPERA staff co-authored a paper, *Recommended Updates to the US EPA Framework for Metals Risk Assessment*, that puts forward a number of technical developments in metals environmental risk assessment for US Environmental Protection Agency (US EPA) to consider in terms of updating their Framework for Metals Risk Assessment, which was released in 2007. US EPA's Metals Framework is highly influential in the US and elsewhere, and the NiPERA publication identifies a number of considerations that should increase the scientific quality of regulatory assessments of metals.

Occupational Exposure Limit Values (OELVs)

New Occupational Exposure Limit Values (OELVs) for both the inhalable and respirable fraction for nickel compounds were adopted by the European Union in March 2022. They are aligned with the scientific opinion of NiPERA and are health-protective and achievable for industry. The OELVs are currently being transposed into national regulations and will enter into force in 2025. The Nickel Institute will continue to monitor transposition into national law. Norway is debating its transposition approach, and NiPERA has provided comments to the Norwegian Labour Inspection Authority in Q3 of 2023. Additionally, NiPERA toxicologists and the Nickel Institute's industrial hygienist have met virtually with toxicologists assigned by the Federation of Norwegian Industries to bring them up to speed on the state of nickel inhalation science and, in particular, the importance of the threshold for effects. Without this contact, NiPERA's scientific position would not be voiced in the multi-party technical discussions in January 2024 where a decision on Norway's OELVs will take place.

Bioavailability-Based Environmental Quality Standards

NiPERA has promoted bioavailability-based standards for nickel in water as an effective approach for ensuring ecosystem protection that is not unnecessarily stringent and expensive. These standards consider the influence of water chemistry on nickel toxicity and also natural background concentrations that vary from region to region. Together, these attributes provide flexibility beyond 'one-size fits-all' approaches that tend to be overly precautionary. NiPERA's collaboration with the US EPA to revise nickel Water Quality Criteria through a Cooperative Research and Development Agreement continued in 2023 with US EPA's release of a draft report summarizing nickel ecotoxicity data that the Agency considers acceptable based on US risk assessment guidance. These data were integrated into the bioavailability models that the US EPA proposes to use. NiPERA provided extensive comments on the draft report. The US EPA acknowledged NiPERA's support and indicated that their peer review of the report had been completed in Q4 2023. A draft of the revised nickel Water Quality Criteria is expected to be released in 2024, and NiPERA will be prepared to review this critically important development.

Elsewhere in the world, NiPERA published a paper validating the use of existing nickel bioavailability models for use in Chinese surface waters as part of our ongoing collaboration with the Chinese Research Academy of Environmental Science, which is a key development in the adoption of bioavailability-based standards for nickel in China. In Japan, NiPERA met with representatives of the Ministry of the Environment to summarize the state of the science for nickel aquatic toxicology and bioavailability to inform their revision of nickel standards.

Impacts of Climate Change and Polar Risk Assessment Initiatives

NiPERA's involvement in assessing the impacts of climate change on environmental risk assessment of metals deepened in 2023 with its participation and leadership in managing a project funded by the International Council on Mining and Metals (ICMM) Materials Stewardship Foundation. The Climate Change Project looks to capitalize on our deep understanding of existing metals risk assessment principles by examining how a changing climate could impact the chemical and physical processes that could alter metal toxicity and bioavailability. The project aims to identify the areas of accepted metals environmental risk assessment frameworks that would require alteration or modification under different climate change scenarios to understand best practices for chemical management. This initiative complements 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. Work with Canadian universities continued in 2023 with the generation of ecotoxicity data for polar species, which will be evaluated to determine if unique risk assessment approaches are required for 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 lifeblood is 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 2023, 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, 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. This work is of continuous importance because REACH data forms the basis for many regulations and legislation in the EU and in other jurisdictions that have adopted the REACH model.

In 2023, newly derived Predicted No Effects Concentrations (PNEC) for freshwater, soil, and marine water were incorporated in the REACH dossiers. The new PNEC values are based on appropriate statistical methods and demonstrate safety for the environment.

The Metals Environmental Exposure Data (MEED) Program, a multi-metallic three-year program managed by Eurometaux, has completed its second year. MEED endeavors to achieve a better understanding of current and future environmental exposures, risks, and management of metals to respond to European regulatory challenges such as the Chemicals Strategy for Sustainability (CSS) and the Zero Pollution Action Plan (ZPAP). NiPERA is one of the 33 MEED program co-sponsors and has a seat on the MEED Steering Team, which provides guidance and technical support.

Achievements from 2023 include the finalization of the municipal sewage treatment plant (STP) exposure assessment project, as well as the regional exposure project. The outcomes of these projects will be incorporated in the REACH dossiers in 2024. The metals mixture project is underway, and preliminary results demonstrate the conservative nature of a Mixtures Allocation Factor (MAF). This is critically important as the application of an MAF has the potential to require companies to reduce emissions or change mitigation measures. Our work on this with other metals associations will continue through mid-2025.

ORGANIZATIONAL STRUCTURE

In January Dr. Ellie Middleton received certification from the International Board of Environmental Risk Assessors (IBERA).

IBERA promotes the conduct of scientifically robust and technically advanced assessments of risks from chemical exposure through the certification of individuals with demonstrated expertise in Environmental Risk Assessment. Ellie's IBERA certification represents a milestone for NiPERA, as now all NiPERA scientists have been recognized by independent professional certification granting boards as experts in their fields.

PEER-REVIEWED NiPERA MANUSCRIPTS

In 2023 NiPERA-sponsored research was well represented in the scientific literature.

Seven peer-reviewed publications were published. All but one include NiPERA staff as co-authors, reflecting their contributions as scientists*.

Environmental Health

2023. Adams WJ, **Garman ER**. *Recommended Updates to the EPA Framework for Metals Risk Assessment: Aquatic Ecosystems*. Integr Environ Assess Manag (accepted for publication August, doi: 10.1002/ieam.4827).

2023. Brix KV, Baken S, Poland CA, Blust R, Pope LJ, Tyler CR. *Challenges and Recommendations in Assessing Potential Endocrine-Disrupting Properties of Metals in Aquatic Organisms.* Environ Toxicol Chem 42(12): 2564-2579.

2023. 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 42(6): 1257-1265.

2023. Merrington G, Gensemer R, Stauber J, Golding L, Smith R, Azizishirazi A, **Schlekat C**, **Garman E**, Ryan A, Cooper C, DeForest D, Peters A. *Implementing approaches to account for metal bioavailability in freshwaters: Current status and future directions*. Integr Environ Assess Manag 19(4): 1147-1151.

2023. 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 42(3): 566–580.

Human Health

2023. **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 13(2): 261.

2023. **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 43(5): 734-751.

**NiPERA/Nickel Institute staff in bold*

BUDGET

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.

Description	Total US Dollars
Revenue	
Nickel Institute Dues	$3,866,517
REACH Project Fees	658,280
Cost Recovery Revenue - Co-Registration	144,100
Interest Income	3,205
Total Revenue	4,672,102
Operating Expenses	
Labor & Fringe	403,380
Administrative Expenses	63,423
Travel	11,274
Research - Nickel Metal	100,358
Research - Nickel Chemicals	93,053
Research - Nickel Alloys	
Research - Occupational Exposure Limits	45,000
Research - Incremental Reach Costs	
Research - Environmental Quality Studies	265,108
Research - Emerging Issues	
Research - Nanoparticulates	225
Research - Nickel Allergic Contact Dermatitis	61,820
Research - Program Support	91,162
Project Travel	67,473
Project Salary & Benefit	1,286,967
Project Office Costs	74,484
REACH	658,278
Transfer Costs	1,154,923
Depreciation Expense	26,205
Total Operating Expenses	4,403,132
Operating Income	**$268,970**

NiPERA

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