NiPERA

NICKEL HEALTH AND ENVIRONMENTAL SCIENCES

2020 ANNUAL REPORT

COVERING ACTIVITIES FROM

JANUARY 1, 2020 – DECEMBER 31, 2020

AND BUDGETARY INFORMATION FOR FISCAL YEAR 2020

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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 2020, 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. Despite setbacks associated with the global COVID-19 pandemic, the 2020 Business Plan was delivered, within budget.

> *2020 will be remembered for the disruption to NiPERA's work routine caused by the COVID 19 situation. NiPERA staff shifted from working collaboratively in our office space to teleworking, and from in-person participation in regulatory discussions on nickel to doing so virtually. Nonetheless, significant achievements were made. The reproductive toxicity study of nickel metal was initiated upon receipt of the European Chemicals Agency's affirmative response to our testing proposal. Significant progress was made in establishing bioavailability-based nickel standards for water in Australia, China, and the USA. Significantly, NiPERA staff and its contractors published 24 peer-reviewed papers in the scientific literature in 2020, demonstrating that NiPERA-sponsored science continues to contribute to regulatory and research activities around the world.*
>
> Dr. Chris Schlekat
> Executive Director, NiPERA Inc.

Science Highlights

Bioavailability-based Environmental Quality Standards

NiPERA continued to play a leading role in the development of bioavailability-based standards for nickel around the world. Bioavailability-based water standards are important because they provide flexibility for industries and municipalities that release nickel without compromising ecological protection.

In ***Australia/New Zealand***, NiPERA teamed with Australian and UK scientists to publish a series of papers that set the stage for establishing a bioavailability-based Water Quality Guideline for nickel. A parallel process was initiated whereby the contents of these papers were submitted to the Australian Department of Agriculture, which is the government agency responsible for reviewing proposals for new guidelines.

In ***China***, NiPERA continued performing research with the Chinese Research Academy of Environmental Sciences to determine the effectiveness of existing bioavailability-based models when applied to standard ecotoxicity test species tested in natural Chinese surface waters. The existing models worked very well, and these results can be used in the next steps in the development of bioavailability-based Water Quality Criteria for nickel in China.

In ***Japan***, NiPERA-sponsored research to generate additional ecotoxicity data that can be considered in the determination of robust Environmental Quality Standards for nickel was published in the peer-reviewed literature, setting the stage for discussions with the relevant authorities.

In ***the USA***, the US Environmental Protection Agency (US EPA) moved ahead with its intentions to develop bioavailability-based approaches for Water Quality Criteria for metals in 2020. A key component of this process was the on-time delivery of nickel bioavailability models to US EPA. The models include empirical-based multiple linear regression models and an updated version of the US biotic ligand model. In December, we learned that manuscripts describing these models were accepted for publication in a peer-review journal. We expect that US EPA's entire package will go to external peer review in 2021, and the fact that the nickel models will be published increases the likelihood of success in the US EPA review process.

Europe is the home to the only existing bioavailability-based Environmental Quality Standard for nickel (Ni EQS). In October, the EU Commission announced that it would review and possibly revise the Ni EQS. The proposed timeline was extremely short, with all technical work to be completed by mid-February 2021. NiPERA suggested that a more appropriate course of action would be to support implementation of the current Ni EQS, to increase the percentage of Member States that can use the bioavailability-based approach as intended. In parallel, NiPERA initiated a review of the recently available data needed to conduct an EQS assessment. By the end of the year, the Commission had not appeared to initiative a review. NiPERA will be prepared to contribute an assessment that reflects the state of the science should the Commission proceed with its review.

Nickel Metal Classification

Extensive activity took place in 2020 to ensure that the classifications of nickel metal are based on scientifically robust assessments. Activity was focused in two areas, addressing i) the lack of robust data on reproductive toxicity for nickel metal, and ii) changes to cancer classification of cobalt metal for all routes (as Carco 1B), which can affect the classification of nickel and its alloys and their use in many essential applications (e.g., food preparation).

In September 2020, the European Chemicals Agency (ECHA) delivered an affirmative decision on the testing proposal for a nickel metal reproductive study. This announcement started the clock in terms of completing the reproductive study before the July 2023 deadline identified in the ECHA decision. The announcement itself is favorable because it prevents precautionary classification based on substandard data. NiPERA launched into full gear to prepare for the study, including identifying and securing the testing material and completing preliminary palatability studies, which are needed to start the dose range finding study in Q1 2021. The outcome of the range finding study will be used to set the parameters of the definitive study that is scheduled to begin in Q3 2021.

In addition, to update the information available on the carcinogenicity of nickel metal, a review of the existing animal and human data was published by external experts. They concluded that the evidence does not support a causal relationship between metallic nickel exposure and respiratory cancer in humans.

With respect to the cobalt carcinogenicity classification, ECHA's opinion that cobalt be classified as Carco 1B for all routes was published in the Official Journal of the EU, and will come into effect in October

2021. While all the evidence points to cobalt metal and soluble cobalt salts being respiratory tract animal carcinogens via inhalation, the classification was applied to "all routes" of exposure due to the lack of studies via the oral route. In order to restrict the classification to the inhalation route, a testing proposal was sent to ECHA to perform an oral carcinogenicity study with cobalt chloride. A negative study with cobalt chloride, the most bioavailable form of cobalt, would also be relevant for cobalt metal. NiPERA agreed to co-sponsor this study as cobalt can be present in nickel metal as an impurity. The testing proposal was submitted to ECHA in May 2020, and we expect a response in 2021.

Alloy Classification

NiPERA and other groups have developed approaches to base alloys classification on the extent with which metals/metalloids are released from alloys as opposed to the concentration of metals within the alloy. 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 developed for a gastric test received support from EURL ECVAM (European Centre for the Validation of Alternative Methods), which then submitted the test protocol to the Organization for Economic Co-operation and Development (OECD) for inclusion into the OECD WNT (Working Group of National Coordinators for the Test Guidelines Programme) test guideline work program for 2020. A favorable outcome was reached in Q2 2020 and an expert sub-group within the WNT was created to draft the guideline. The OECD WNT is expected to finalize the test guideline in 2022. In addition, discussions at the EU Competent Authorities for REACH and CLP (CARACAL) level on the regulatory applicability of metal release data to refine the classification of alloys were initiated in Q2 2020 and are expected to continue into 2021. Metal commodities are starting to publish data on metal release from alloys, which will support implementation of this approach.

Nickel Nanoparticulate Research Program Progresses

The Nickel Nanoparticulate proactively addresses current toxicological data gaps and risk characterization issues specific to nanoforms of nickel metal and compounds. In 2020, a comprehensive critical review of the existing environmental literature on nickel nanoparticles was published in the peer-review journal *Environmental Toxicology and Chemistry.* Four NiPERA scientists served as co-authors on this paper, which importantly concluded that aquatic organisms are not more sensitive to nickel nanoparticles than to dissolved forms of nickel. This sets the stage for read across options should producers of nickel nanoparticles decide to register them in REACH-like legislations.

Food Contact Materials

In 2020, the European Food Safety Authority (EFSA) revised its 2015 opinion on nickel in food and drinking water, increasing the chronic Tolerable Daily Intake (TDI) value from 2.8 to 13 µg Ni/kg body weight/day. A NiPERA-sponsored peer reviewed publication together with new EFSA guidance on the application of Benchmark Dose analysis are likely to have contributed to the more realistic 2020 assessment with the chronic TDI value, which now matches the one set by World Health Organization. EFSA values are used to derive regulatory standards, such as limits for nickel in drinking water and nickel release from food contact material. Based on this revised opinion, the safe use of nickel-containing stainless steel in food and beverage applications is likely to be preserved.

Region-specific Environmental Risk Assessment of Nickel (From Tropical to Polar Regions)

The Tropical Environmental Risk Assessment Program began in 2014 in recognition of the increasing importance of tropical areas for the future of nickel production. By completing the research phase of the project, NiPERA achieved the principal goal of establishing approaches that can be used to perform ecological risk assessments of nickel in tropical ecosystems that are founded on region-specific data and are free of undue application of precaution. A synthesis of the 15 detailed peer-reviewed publications from the program was accepted for publication in the journal I*ntegrated Environmental Assessment and Management* in late 2020. Among the takeaways established in this paper are that tropical ecosystems are not uniquely sensitive to nickel, and the identification of building blocks from which ecological risk assessments in tropical areas can be performed.

In 2020, NiPERA began to pivot its focus from the increasingly important tropical region to polar regions. Polar regions have historical importance for nickel production, and they offer parallels to tropical regions in terms of the relevance of traditional ecological risk assessment approaches. That is, are traditional approaches adequate, and if they are not, what needs to be done to fill the identified data gaps? NiPERA began the Polar Environmental Risk Assessment Program by performing a critical review of the available literature. The draft review identified that few data are available on the sensitivity of polar species to nickel, and that one of the factors contributing to this is the nature of organisms that occur in cold climates – they develop slowly, and are difficult to test in the laboratory. We anticipate the critical review to be published in 2021, when we will begin the development of the next steps in the research program in concert with Nickel Institute members that operate in polar environments.

Copyright Compliance

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 2020, NiPERA began the process of shifting from its traditional approach to obtaining peer-reviewed articles to a new approach that ensures that the process by which we obtain articles unequivocally complies with copyright law. NiPERA established an agreement with Copyright Clearance Center to implement RightFind Enterprise, which is a one-source, web-based platform that integrates copyright licensing with the management of NiPERA's publications. In order to make RightFind operational, an enormous effort was undertaken to upload nearly 15,000 existing publications from the NiPERA document storage server to the RightFind platform. Early in 2021 we expect to implement RightFind for all scientific staff.

EU REACH

In Europe, the Nickel Institute acts as the Secretariat for the Nickel Consortia. In 2020 we continued collaboration with ECHA on the Metals and Inorganics Sectorial Approach (MISA). This cooperative program aims to resolve outstanding technical and methodological issues of relevance for metals and inorganics as well as improve the compliance and quality of the dossiers. Moreover, it provides a good forum to engage with ECHA on open scientific and regulatory questions. In 2020, the Nickel Consortia MISA workplan focused mainly on the implementation of lessons learned during the 2019 MISA workshops on information requirements for environmental endpoints and on compliance of registration dossiers for complex inorganic substances. In parallel, additional workshops were organized in 2020 with

a focus on exposure assessments throughout the whole substance's life cycle and with particular attention to occupational exposure assessments.

The Nickel REACH Consortia have been diligently and continuously improving and updating the registration dossiers. The current approach is to perform detailed updates every other year. Additionally, the MISA priorities are widely integrated in our workplan. We remain committed to deliver good quality and updated registration dossiers for nickel and nickel substances. These are important as they form the basis for many regulations and legislation in the EU and abroad, especially Asia, where some countries are adopting REACH like chemical management programs.

Korea REACH

Following the registration of nickel compounds in Korea, the Nickel Institute has ensured that classification proposals take into account and correctly interpret the most recently available scientific data. NiPERA has also ensured that despite no categorization of carcinogenicity by route of exposure in Korea, the authorities recognize that the classification of nickel compounds as carcinogens is restricted to the inhalation route only for risk assessment purposes.

Peer Reviewed NiPERA Manuscripts

Despite the challenges that 2020 presented to NiPERA staff and our scientific collaborators, NiPERA-sponsored research was extremely well represented in the scientific literature. A total of 24 peer-reviewed publications were published in 2020, and many of these include NiPERA staff as co-authors, which reflects their contributions as scientists.

Human Health Publications

2020. Basketter D. Nickel: Intrinsic Skin Sensitization Potency and Relation to Prevalence of Contact Allergy. Dermatitis (epub Aug 19). doi: 10.1097/DER.0000000000000666.

2020. Buxton S, Voges Y, Donath C, Oller A. Gene (HPRT) and chromosomal (MN) mutations of nickel metal powder inV79 Chinese hamster cells. Mutat Res Fund Mol Mech Mutagen (819-820) 111688.

2020. Delbeke K, Baken S, Perez Simbor L, Rodriguez PH, Brouwers T, Verougstraete V, Binks S, Oller A, Danzeisen R, Gilles M. Copper alloys' metal migration and bioaccessibility in saliva and gastric fluid. Regul Toxicol Pharmacol 117: 104754. doi: 10.1016/j.yrtph.2020.104754.

2020. Dutton MD, Thorn R, Lau W, Vasiluk L, Hale B. Gastric bioaccessibility is a conservative measure of nickel bioavailability after oral exposure: Evidence from Ni-contaminated soil, pure Ni substances and Ni alloys. Environ Pollut Epub Oct 14.

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. Prueitt RL, Li W, Chang Y-C, Boffetta P, Goodman JE. Systematic review of the potential respiratory carcinogenicity of metallic nickel in humans. Critical Reviews in Toxicology 50(7): 605-639.

Environmental Health Publications

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. 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.

2020. Crémazy A, Brix KV, Smith DS, Chen W, Grosell M, Schlekat CE, Garman ER, Middleton ET, Wood CM. A Mystery Tale: Nickel Is Fickle When Snails Fail—Investigating the Variability in Ni Toxicity to the Great Pond Snail. Integrated Environmental Assessment and Management 16(6) 983-997.

2020. Gillmore ML, et al. Effects of dissolved nickel and nickel-contaminated suspended sediment on the scleractinian coral, Acropora muricata. Marine Pollution Bulletin 152: 110886.

2020. Gissi F, Wang Z, Batley GE, Leung KM, Schlekat CE, Garman ER, Stauber JL. Deriving a Chronic Guideline Value for Nickel in Tropical and Temperate Marine Waters. Environmental toxicology and chemistry 39(12): 2540-2551.

2020. Mano H, Shinohara N. Acute Toxicity of Nickel to Daphnia magna: Validation of Bioavailability Models in Japanese Rivers. Water, Air, & Soil Pollution 231(9): 1-11.

2020. Mano H, Shinohara N, Naito W. Reproduction Sensitivity of Five Daphnia Species to Nickel. Journal of Water and Environment Technology 18(6): 372-382.

2020. Meyer JS, Lyons-Darden T, Garman ER, Middleton ET, Schlekat CE. Toxicity of Nanoparticulate Nickel to Aquatic Organisms: Review and Recommendations for Improvement of Toxicity Tests. Environmental Toxicology and Chemistry 39(10): 1861-1883.

2020. Peters A, Merrington G, Stauber J, Golding L, Batley G, Gissi F, Merrin A, Binet M, McKnight K, Schlekat CE, Garman E, Middleton E. Empirical bioavailability corrections for nickel in freshwaters for Australia and New Zealand water quality guideline development. Environmental Toxicology and Chemistry 40(1) 113-126.

2020. Peters A, Nys C, Merrington G, Verdonck F, Baken S, Cooper CA, Van Assche F, Schlekat C, Garman E. Demonstrating the Reliability of bio-met for Determining Compliance with Environmental Quality Standards for Metals in Europe. Environmental Toxicology and Chemistry 39(12): 2361-2377.

2020. Soucek DJ, Dickinson A, Schlekat C, Van Genderen E, Hammer EJ. Acute and Chronic Toxicity of Nickel and Zinc to a Laboratory Cultured Mayfly (Neocloeon triangulifer) in Aqueous but Fed Exposures. Environmental Toxicology and Chemistry 39(6)1196-1206.

2020. Stauber J, Golding L, Peters A, Merrington G, Adams M, Binet M, Schlekat C. Application of Bioavailability Models to Derive Chronic Guideline Values for Nickel in Freshwaters of Australia and New Zealand. Environmental Toxicology and Chemistry 40(1): 100-112.

2020. Wang N, Kunz JL, Cleveland DM, Steevens JA, Hammer EJ, Van Genderen E, Ryan AC, Schlekat CE. Evaluation of Acute and Chronic Toxicity of Nickel and Zinc to 2 Sensitive Freshwater Benthic Invertebrates Using Refined Testing Methods. Environmental Toxicology and Chemistry 39(11): 2256-2268.

2020. Wang Z, Yeung KW, Zhou GJ, Yung MM, Schlekat CE, Garman ER, et al. Acute and chronic toxicity of nickel on freshwater and marine tropical aquatic organisms. Ecotoxicology and Environmental Safety 206: 111373.

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.

Below is the table from the 2020 annual report.

Description	Total USD
Revenue	
Nickel Institute Dues	$3,576,045
Cost Recovery Income	75,000
Total Revenue	*3,651,045*
Operating Expenses	
Labor & Fringe	172,273
Administrative Expenses	41,754
Travel	6,688
Research - Nickel Metal	322,070
Research - Nickel Chemicals	44,437
Research - Nickel Alloys	53,240
Research - Occupational Exposure Limits	0
Research - Environmental Quality Studies	209,687
Research - Emerging Issues	103,562
Research - Nanoparticulates	5,831
Research - Nickel Allergy Contact Dermatitis	0
Research - Program Support	136,485
Project Travel	0
Project Salary & Benefit	1,296,482
Project Office Costs	92,730
Transfer Costs	1,087,392
Depreciation Expense	58,935
Total Operating Expenses	*3,631,566*
Operating Income	**$19,479**

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